Pancreatitis

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Key Points

1. Pancreatitis is inflammation of the pancreas, which can be classified as acute, acute recurrent, or chronic pancreatitis. However, this condition may be more easily considered based on etiology, as there is a myriad of potential causes of pancreatitis in the pediatric population, from developmental anatomical abnormalities to rising incidence of obesity. Subtypes of pancreatitis include necrotic and hemorrhagic.
2. Acute pancreatitis results from ectopic activation of pancreatic enzymes. In contrast, chronic pancreatitis is a continuing inflammatory process of the pancreas, characterized by irreversible morphologic changes (i.e. calcifications, fibrosis, ductal stricture, dilatation), which may lead to exocrine and endocrine insufficiency.
3. The risk of recurrent pancreatitis in the pediatric population has been estimated at 15–30%. This may lead to chronic pancreatitis, thus highlighting the importance of prompt recognition and treatment of pancreatitis in its acute phase.

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C. P. Coppola et al. (eds.), *Pediatric Surgery*,
https://doi.org/10.1007/978-3-030-96542-6_71

4. Current practice utilizes a staged approach to the treatment of pancreatitis in children, with endoscopic intervention prior to consideration of open surgical techniques.
5. While the need for surgical intervention for pancreatitis in the pediatric population is uncommon, consideration should be made for cases of failed medical and endoscopic management (often with multiple hospitalizations), chronic pain, obstructing stones, and other complications such as pseudocysts and strictures. The goal of surgery in these cases is to improve quality of life, address the pathophysiologic complications of pancreatitis, and to preserve the integrity of the pancreas as an endocrine and exocrine organ.

1. *Background*
   a. Epidemiology
      i. Pancreatitis is an uncommon disease in the pediatric population, and its etiologies are more diverse compared to adults.
      ii. Males and females are equally affected.
      iii. Overall mortality rate of pancreatitis in the general population is 10%, and this increases to 50% with hemorrhagic pancreatitis.
   b. Etiologies
      i. While most cases of acute and chronic pancreatitis are idiopathic, the most common identifiable etiologies of *acute pancreatitis* are listed below:
         1. Abdominal trauma, including non-accidental trauma (NAT, child abuse) and iatrogenic cause following endoscopic retrograde cholangiopancreatography (ERCP)
         2. Biliary disease, including choledocolithiasis, gallstone pancreatitis
         3. Congenital abnormalities
            a. Pancreas divisum
            b. Annular pancreas
            c. Heterotopic pancreas, most commonly in the duodenum
            d. Choledochal cyst
         4. Multisystem disease
         5. Drugs and toxins, i.e., ethanol, L-asparaginase, Valproic acid, Azathioprine, Mercaptopurine, Mesalamine, steroids
         6. Viral infection
      ii. Although there are many shared etiologies between acute and chronic pancreatitis, cases of *chronic pancreatitis* involve a higher representation of genetic conditions, as listed below:

1. Cystic Fibrosis (CFTR mutation, autosomal recessive)
2. Hereditary pancreatitis (PRSS1 mutation: cationic trypsinogen, autosomal dominant)
3. Metabolic disorders, i.e., hypertriglyceridemia
4. Autoimmune pancreatitis
5. Juvenile tropical pancreatitis
6. Chronic fibrosing pancreatitis
7. Pancreatic tumors

2. *Pathophysiology*

a. Developmental anatomy

i. Ventral/dorsal pancreatic bud: at 6 weeks *in utero*, the ventral bud rotates posteriorly, to the right, and clockwise, thereby fusing with the dorsal bud.

1. Ventral bud = uncinate process, inferior portion of head of pancreas

a. Duct of Wirsung- main pancreatic duct that merges with common bile duct, then drains into duodenum at Ampulla of Vater, via Sphincter of Oddi

2. Dorsal bud= body, tail, superior portion of head of pancreas

a. Duct of Santorini- accessory duct that drains into duodenum via accessory papilla

ii. Annular pancreas

1. Failure of clockwise rotation of the ventral bud results in duodenal obstruction of the D2 segment by the pancreas or band, which can lead to pancreatitis.

iii. Pancreas divisum

1. Failure of fusion of pancreatic Ducts of Wirsung and Santorini results in the majority of pancreatic enzymes draining via the accessory papilla. Stenosis of the Duct of Santorini may also be present, causing pancreatitis.

b. Endocrine function

i. Alpha cells secrete glucagon
ii. Beta cells secrete insulin
iii. Delta cells secrete somatostatin, vasoactive intestinal peptide (VIP)
iv. PP or F cells secrete pancreatic polypeptide
v. Gastrin-producing cells present in fetal pancreas only

c. Exocrine function: amylase, lipase, trypsinogen, chymotrypsinogen, carboxypeptidase, bicarbonate

i. Ductal cells secrete HCO3—(contain carbonic anhydrase)
ii. Acinar cells secrete digestive enzymes (listed above)

iii. Amylase is the only pancreatic enzyme listed above that is secreted in its active form; the rest require chemical conversion into their active forms.

d. Hormonal control of enzymatic secretion

i. Acetylcholine (ACh) and secretin cause an increase in bicarbonate.
ii. CCK and ACh cause an increase in secretion of pancreatic enzymes.
iii. Somatostatin and glucagon cause a decrease in pancreatic exocrine function.

e. In Cystic Fibrosis, the genetically abnormal CFTR membrane protein results in NaCl transport dysfunction, affecting submucosal glands (sinopulmonary disease, Type 1 diabetes) and exocrine epithelial cells. Thick secretions obstruct exocrine ducts, which destroy pancreatic acinar cells. This leads to pancreatitis, and in severe cases, pancreatic insufficiency with malabsorption and failure to thrive.

3. *Clinical presentation*

a. Classically, pancreatitis presents as acute onset epigastric pain with radiation to the central back. The pain tends to be positional. This may be accompanied by nausea, vomiting, anorexia, abdominal distention, ileus, jaundice (with gallstones or obstruction), fever, tachycardia, and hypotension.
b. On physical examination, one may find signs of abdominal trauma, tenderness, distention, or peritoneal signs. In cases of hemorrhagic pancreatitis, Grey Turner's sign (bluish discoloration of flanks) and/or Cullen's sign (bluish discoloration of periumbilical region) may be present. This is due to infiltration of blood along subcutaneous planes and the gastrohepatic and falciform ligaments respectively, as the pancreas is a retroperitoneal organ.
c. Chronic pancreatitis may mimic acute pancreatitis. It typically presents as chronic abdominal pain that is difficult to treat. It may be accompanied by signs of pancreatic exocrine and endocrine insufficiency, such as diabetes with labile blood sugars, steatorrhea, diarrhea, ADEK vitamin deficiency, anorexia, and failure to thrive.

4. *Diagnosis*

a. Several classification systems for pancreatitis have been utilized in the clinical setting.

i. The Atlanta classification (revised in 2012) characterizes acute pancreatitis by an early (<2 weeks) and late (>2 weeks) phase, with mild, moderate, and severe cases.
ii. Specific to pediatrics, Morinville et al. in 2012 described the INSPPIRE criteria for diagnosis of acute pancreatitis with any two of these: abdominal pain, or imaging consistent with pancreatitis, or lipase/amylase 3 times the upper limit of normal.

iii. Modified Ranson criteria may be used for a pediatric scoring system, though ongoing efforts are being made to explore the utility of current prediction severity tools published in the adult population by adding pediatric systemic inflammatory response syndrome (SIRS) score, age, and weight.

b. If pancreatitis is suspected based on history and physical examination, amylase and lipase should be measured, and other laboratory values may also be useful in establishing the diagnosis.

i. Serum amylase and lipase (more specific) tend to be at least 3× the upper limits of normal.
ii. While amylase is a non-specific indicator of pancreatitis, amylase-P is a laboratory test available at some centers, whose specificity is closer to that of lipase.
iii. Other lab findings may include: leukocytosis, hyperglycemia, hypocalcemia, hypertriglyceridemia, hypoalbuminemia, hyperbilirubinemia, elevated LFTs, acidosis, glycosuria.
iv. Sweat chloride and modern genetic testing will be utilized in cases where there is suspicion of syndromic or genetic basis for the illness.

c. Imaging studies provide evidence of structural changes in the glands or ducts. Transabdominal ultrasonography, CT, MRCP, ERCP, and EUS may be utilized, and provide evidence of acute vs. chronic changes.

i. Ultrasound (US) is a primary screening tool, and its findings may reveal a diffusely enlarged or edematous pancreas with dilated pancreatic ducts, peri-pancreatic fluid collection, abscess, or pseudocyst.
ii. CT may be utilized for evaluation of abnormalities found on US; chronic pancreatitis, pancreatic necrosis, complications, pancreatic trauma, or neoplastic disease process. CT findings include an enlarged gland with ill-defined margins, peri-pancreatic fluid collection, areas of decreased or enhanced density, or pseudocyst.
iii. Magnetic resonance cholangiopancreatography (MRCP) is a non-invasive imaging study of biliary tree and surrounding structures, is more sensitive than CT, and helps delineate an anatomical lesion. In children, this imaging modality frequently requires sedation.
iv. Endoscopic retrograde cholangiopancreatography (ERCP) is an invasive modality that can help diagnose various pancreatic and biliary anomalies, ductal abnormalities, or obstructions. It can also serve as a therapeutic intervention, i.e., sphincterotomy and stent placement.

5. *Initial management*

a. The management of acute pancreatitis usually consists of supportive and medical therapy with IV fluid hydration and pain control. Initial management is directed at stabilizing the patient and aggressive hydration measures to help

decrease the risk of multi-organ failure. This should include strict measurement of ins and outs, and serial labs as indicated.

b. Bowel rest with parenteral nutrition versus enteral nutrition has been a topic of much debate and research in the adult population. In adults, meta-analyses of practices regarding nutrition in pancreatitis have clearly shown that enteral over parenteral nutrition reduces mortality, incidence of multisystem organ failure, and need for invasive procedures. The data has not been as heavily explored in the pediatric population, but current practice does support the implementation of early enteral feeding, within 24–48 h following admission. In fact, if during the course of a pancreatitis episode the patient develops the desire to eat, this may be a sign that the severe pancreatic inflammation has begun to resolve.

c. In cases of severe pancreatitis, total parenteral nutrition (TPN) may be necessary if the patient cannot tolerate enteral feeds, or in conjunction with feeding.

   i. Jejunal feeds via small bore feeding tube are preferred over TPN due to lower complication rates and lower costs.

   ii. In cases of chronic pancreatitis, low-fat meals and pancreatic enzyme supplements may help restore exocrine enzyme deficiencies.

6. *Treatment*

   a. Pancreatitis prevention

      i. In cases of hereditary pancreatitis or a known predisposition based on genetic markers, it may be useful to supplement diet with fibrates, fish oil, and abstain from alcohol.

      ii. Congenital abnormalities of the pancreas have the potential to cause pancreatitis. However, these conditions are typically diagnosed early in life and their unique interventions will ideally reduce the chances of developing pancreatitis.

         1. Annular pancreas presents with signs and symptoms of duodenal obstruction (nausea, vomiting, abdominal pain; X-ray with double bubble sign). Options for surgical intervention are duodenojejunostomy or duodenduodenostomy *without* resection of the pancreas.
         2. Pancreas divisum may present with pancreatitis, but most cases are asymptomatic. Both diagnosis and treatment utilize ERCP with sphincteroplasty. In this procedure, canalization of the minor papilla will reveal a long, large duct of Santorini, while canalization of the major papilla will reveal a short duct of Wirsung.

   b. Medical treatment

      i. Diabetes screening and management, including yearly glucose and hemoglobin A1C

      ii. Early identification and treatment of fat-soluble vitamin deficiencies

         1. Patients typically require antacid medication in addition to pancreatic enzyme supplementation to assist with breakdown.

c. Pancreatitis procedures

i. ERCP or EUS may be useful in mitigating threats of continued pancreatic damage from obstruction at the common bile duct or pancreatic duct.

1. For example, ERCP is the mainstay of treatment for gallstone pancreatitis with obstruction stones, as evidenced by persistently elevated bilirubin/LFTs, and dilated ducts on US or MRCP.
2. Patients with gallstone pancreatitis require interval cholecystectomy when pancreas inflammation has resolved.

ii. Surgical management of pancreatitis is rarely required, and it is reserved for cases of chronic, relapsing pancreatitis, failed conservative medical therapy, intractable pain, impaired nutrition, and narcotic addiction.

iii. Surgical reconstructive options include distal pancreatectomy with Roux-en-Y pancreaticojejunostomy (Duval procedure), and lateral pancreaticojejunostomy (Puestow procedure) with or without anterior resection of the pancreatic head (Frey procedure).

iv. Laparoscopic or open surgical debridement is indicated for infected pancreatic abscess or necrosis, and emphysematous pancreatitis.

v. Video-assisted retroperitoneal debridement (VARD procedure) has been developed more recently in the treatment of chronic severe pancreatitis in adults, as a blend of endoscopic retroperitoneal necrosectomy and open surgery.

vi. In patients with Cystic Fibrosis, pancreas transplantation may be indicated, in addition to double lung transplantation.

7. *Outcomes*

a. Early complications—days to weeks

i. Development of ARDS due to pro-inflammatory mediators, including phospholipase, causing capillary leakage. This non-cardiogenic pulmonary edema can usually be diagnosed with chest X-ray (CXR) and may require intubation for ventilator support.

ii. Pancreatic saponification due to enzymatic breakdown of the tissue can lead to pancreatic necrosis. The saponification reaction also results in hypocalcemia. Diagnose with ionized calcium level, and replete with IV calcium.

iii. Infected pancreatic necrosis with systemic inflammatory response syndrome (SIRS)

1. This is diagnosed by CT-guided tissue biopsy (performed to rule out malignancy) and culture (to guide the use of antibiotics) and ultimately requires surgical debridement as described in treatment.
2. Carbapenems (Imipenem, Meropenem) are preferred over ciprofloxacin in the treatment of infective pancreatitis.

iv. Ascites and pleural effusions are due to retroperitoneal leakage of pancreatic fluid. These collections seen on US and CXR should not be drained unless there is a concern for infection, as they will resolve as the disease process is addressed.

b. Late complications—weeks to months

i. Pancreatic pseudocyst formation

1. A pseudocyst is *not* epithelial-lined; commonly forms in the head of the pancreas
2. Can cause mass effect resulting in early satiety, abdominal fullness, and even small bowel obstruction
3. Typically resolve spontaneously
4. Treatment is based on size and timing:

a. If the pseudocyst is <6 cm AND has been present for >6 weeks, watch and wait.
b. If it is >6 cm OR >6 weeks, perform drainage with biopsy (EGD or percutaneous).
c. Once the pseudocyst has formed a mature wall, OR if growing over time, perform percutaneous vs. open cystogastrostomy.

ii. Pancreatic fistulas usually arise from complications of pancreatic operations.

1. Spontaneous closure in low output fistulas (<200 cc/day)
2. Treatment involves NPO with TPN and octreotide, but ERCP with pancreatic stenting may be needed if fistula fails to close.

iii. Pancreatic abscesses are treated with surgical drainage and antibiotics.
iv. Mechanical obstruction of duodenum and common bile duct
v. Splenic vein thrombosis with portal hypertension

1. Gastric varices may form as collaterals. Splenectomy is indicated for isolated bleeding varices.

vi. Splenic artery pseudoaneurysm
vii. Pancreatic insufficiency

1. This is an unfortunate sequela of chronic pancreatitis, and typically exocrine function of the pancreas is more impacted than endocrine function.
2. Adherence to a diet high in carbohydrates and protein, and low in fat along with enzymatic supplementation is important, but ultimately, these patients need pancreas transplantation.

Additional Notes

The rising incidence of pancreatitis in children is thought to be due to increasing obesity and drug abuse rates in this population, and also perhaps due to improved detection strategies. While classic causes of pancreatitis in adults like alcohol, gallstones, iatrogenic trauma, and medication reactions may be seen in pediatric cases, the consideration of congenital etiologies- from anatomic anomalies to genetic disorders of metabolism- significantly expands the differential. Although over time several classification models have been developed for the diagnosis of this condition, a laboratory value of lipase 3× the upper limit of normal remains a strong indicator of pancreatitis. Imaging by CT is not necessary if symptoms and lab values correspond to a diagnosis of pancreatitis, as early pancreatitis may not be visualized on such imaging; rather, obtain confirmatory imaging to assist with diagnosis in cases where lab values are equivocal. Although the pancreas is poorly visualized on ultrasound, this test may be useful in cases of gallstone pancreatitis for visualization of the gallbladder. Similarly, MRCP is useful to identify certain etiologies of pancreatitis, including stricture and malignancy.

Necrotizing pancreatitis has historically resulted in high complication rates and mortality, which has brought about the development of what is known as the "step up pathway," or staged approach. Even within this model, there is an ongoing debate around the myriad options of endoscopic, laparoscopic, open, and blended techniques that are being utilized to address such severe cases of pancreatitis. When medical treatment fails, often therapeutic endoscopy is first-line interventional treatment and is intended to serve as source control and mitigation of sepsis. Options include endoscopic cystgastrostomy with or without stent or pigtail drain placement. Depending on etiology of pancreatitis, presence of anatomical abnormalities, and gene mutation status, appropriate surgical intervention may be explored next. If endoscopic treatment is unsuccessful in mitigating disease, definitive procedures in the step-up approach include pseudocyst drainage, more specifically cystogastrostomy or cyst-enterostomy requiring Roux-en-Y reconstruction; partial pancreatectomy, total pancreatectomy with islet autotransplantation; and longitudinal pancreaticojejunostomy (Puestow procedure) with or without anterior resection of the pancreatic head (Frey procedure). The VARD procedure (video-assisted retroperitoneal debridement) was described in 2007 by Van Santvoort et al. as a blend of endoscopic retroperitoneal necrosectomy and open surgery in the step-up approach to necrotizing pancreatitis in adults, using a left subcostal incision to remove necrotic pancreatic tissue and laparoscopic identification of deeper areas of necrosis, followed by continuous lavage of the retroperitoneum in the post-operative period. Ultimately, the step-up approach aims to achieve long-term pain relief and preserve maximal pancreatic function while minimizing surgical trauma in critically ill patients. Fortunately, this severity of disease progression is seen much more rarely in the pediatric population.

During the novel coronavirus disease 19 (COVID-19) pandemic, some attention has been drawn to understand the extrapulmonary manifestations of this disease, including that of acute pancreatitis. While a causal relationship between pancreatitis and COVID-19 has not been proven, temporal association between the two is identified in several case reports in adults, and a few in children to date. In these pediatric case reports, adolescent patients developed symptoms of acute pancreatitis within 1 week of suffering from COVID-19 illness. As development of pancreatitis has been observed in a constellation of viral diseases (including measles, mumps, EBV, Coxsackievirus), a connection to immune-mediated pancreatic injury or angiotensin-converting enzyme 2 involvement in the setting of COVID-19 infection may be plausible, though this idea requires further investigation.

Study Questions

1. A 6-year-old male with past medical history significant for prematurity and NEC is being evaluated in the PICU for newly diagnosed gallstone pancreatitis. He is severely dehydrated and requires aggressive pain control measures. What is the best approach in regards to nutritional management of the patient?

   a. Enteral feeds in 1 week
   b. Enteral feeds in 24–48 h
   c. TPN immediately
   d. Enteral feeds immediately

   Answer: (b.) Enteral feeds in 24–48 h. Historical practice in the medical management of acute pancreatitis stressed the importance of bowel rest in order to rest the exocrine pancreas to prevent further inflammation and local destruction. More recently, practice has shifted toward early initiation of enteral feeding with positive outcomes in these patients.

2. On hospital day #10 in a 16-year-old male admitted with abdominal pain secondary to hereditary pancreatitis, the patient develops fever and tachycardia with leukocytosis. Interval CT scan demonstrates development of gas pockets within the body of an inflamed pancreas with areas of necrosis. What is the most appropriate next step in the treatment of this patient?

   a. Immediate percutaneous drainage
   b. VARD procedure
   c. Transfer to PICU with close monitoring including serial abdominal exams
   d. Initiate IV antibiotics alone

   Answer: (a.) Immediate percutaneous drainage. Although initiation of antibiotics is warranted, given the patient's fever and elevated WBC count, it is also necessary to achieve source control in this case of infected pancreatic necrosis. At the time of drain placement, tissue biopsy and culture are useful to rule out malignancy and guide antibiotic selection.

3. A 5-month-old male presents to the emergency department with fussiness, abdominal distention, non-bilious vomiting, and anorexia that began 1 day ago. Ultrasound demonstrates a proximal narrowing past the pylorus. What laboratory studies may help distinguish the likely diagnosis from other conditions that may present with similar symptoms?

   a. Electrolytes
   b. Blood smear
   c. Amylase, lipase
   d. Liver function tests

   Answer: (c.) Amylase, lipase. The differential in an infant with these symptoms on presentation is wide, but description of the vomitus and imaging are helpful in working toward an appropriate diagnosis. Abnormally elevated amylase or lipase 3× above the upper limit of normal, along with the above US findings, suggests a congenital abnormality resulting in pancreatitis in this patient. Electrolyte abnormalities may be seen in hypertrophic pyloric stenosis, along with projectile bilious vomiting. Blood smear may be revealing in a patient with a blood-borne illness, whether viral or hereditary. Abnormal LFTs are typically accompanied by jaundice in cases of biliary disease.

Further Reading

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