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Educational Gaps

1. The incidence of acute pancreatitis has increased in pediatric patients over the past two decades, approaching the incidence in adults.
2. While pancreatic rest, antiemetics, analgesia, fluid support, and monitoring for complications remain the mainstays of acute pancreatitis management, clinicians should know that approaches to pancreatic rest and fluid management have changed, as have long-time teachings on the use of opiods and the institution of nutrition.

Objectives

After completing this article, readers should be able to:

1. Differentiate between acute and chronic pancreatitis.
2. Know how to diagnose acute pancreatitis.
3. List common causes for acute, recurrent, and chronic pancreatitis.
4. Explain the utility of clinical symptoms, biochemical testing, and radiographic imaging in diagnosing acute and chronic pancreatitis.
5. Understand the management of acute pancreatitis and chronic pancreatitis.

Introduction

Pancreatitis is an inflammatory condition of the pancreas. Two major forms of pancreatitis, acute and chronic, are recognized. Acute pancreatitis is a reversible process, whereas chronic pancreatitis (CP) is irreversible. Acute pancreatitis is more prevalent, and most patients have a single episode of pancreatitis. A small number of patients have recurrent episodes of acute pancreatitis and are at risk of developing CP.

Pancreatitis in pediatric patients is an increasingly recognized disorder. Although standard diagnostic criteria for pancreatitis exist, their intricacies deserve close attention, especially in pediatrics. Research over the past decade has demonstrated differences between pancreatitis in children and adults, particularly in presentation, etiology, prognosis, and nature of acute recurrent pancreatitis (ARP). Many of the traditional thoughts about management have been challenged, and the treatment of pancreatitis is evolving.

Abbreviations

ARP:	acute recurrent pancreatitis
CFTR:	cystic fibrosis transmembrane conductance regulator
CP:	chronic pancreatitis
CT:	computed tomography
ERCP:	endoscopic retrograde cholangiopancreatography
EUS:	endoscopic ultrasound
IgG4:	immunoglobulin G4
MRCP:	magnetic resonance cholangiopancreatography
PRSS-1:	cationic trypsinogen gene
SPINK-1:	serine protease inhibitor Kazal type 1
TPN:	total parenteral nutrition

Acute Pancreatitis in Pediatrics

Epidemiology

Acute pancreatitis occurs in all age groups, even in infants. Recent studies from the United States, Mexico, and Australia have reported an increasing incidence of pediatric acute pancreatitis over the past 2 decades. (1) Currently, the best estimates suggest that there are 3.6 to 13.2 pediatric cases per 100,000 individuals per year, an incidence that approaches the incidence of disease in adults. Much of the increased diagnosis of acute pancreatitis results from greater physician awareness, as evidenced by a concurrent increase in biochemical testing (amylase and lipase levels) for pancreatitis.

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Pathophysiology

Acute pancreatitis results from injury of the pancreas and a subsequent inflammatory response that may involve adjacent and distant tissues and organs. The prevailing theory of the pathophysiology of pancreatitis includes several distinct steps. First, an event initiates a process of acinar cell injury. The cell injury produces pancreatic edema and a local inflammatory response, with release of inflammatory mediators. The production of cytokines and chemokines provoke a systemic inflammatory response. The magnitude of this inflammatory response determines the clinical severity of acute pancreatitis and can lead to complications such as pancreatic necrosis, shock, and distant organ failure.

Much current research focuses on the nature of the acinar cell injury. The prevailing model is that nonphysiologic calcium signals initiate the premature intracellular activation of trypsinogen to trypsin (Fig 1). Trypsin, in turn, activates other digestive proenzymes. The activated digestive enzymes then mediate acinar cell injury. Recently, this autodigestion model has been challenged. In some, if not all, patients with pancreatitis, an aberrant unfolded protein response and the resultant endoplasmic reticulum stress may initiate apoptotic pathways and inflammatory signals. (2)

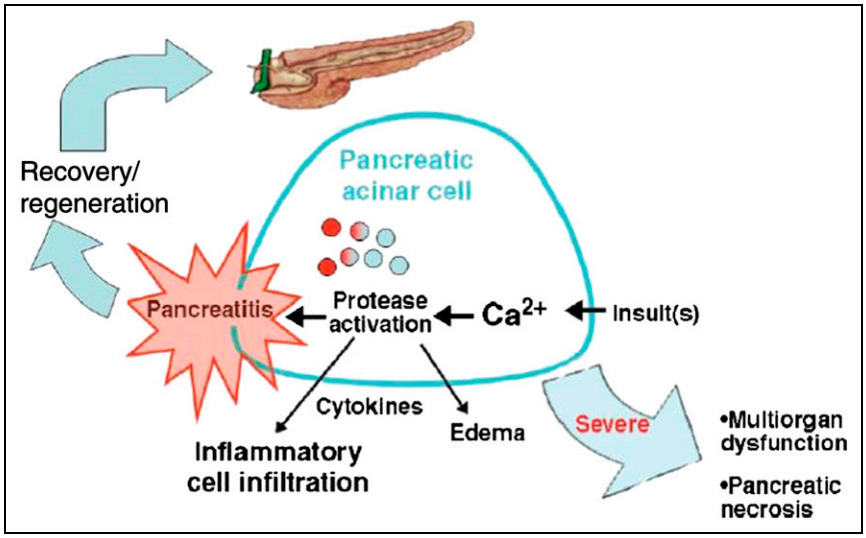

Figure 1. Pathophysiology of acute pancreatitis. Multiple causes of acute pancreatitis can lead to abnormal intra-acinii calcium signaling. This signaling leads to intra-acinar zymogen activation and resulting pancreatic injury and cytokine response, as well as potential systemic inflammatory response. Ca^{2+} = calcium. Reprinted with permission from Bai HX, Lowe ME, Husain SZ. What have we learned about acute pancreatitis in children? *J Pediatr Gastroenterol Nutr*. 2011;52(3):263 (License Number: 2886070809948).

Table 1. Causes of Acute Pancreatitis in Children

Common
Biliary disorders
Systemic conditions
Medications
Trauma
Idiopathic
Less common
Infection
Metabolic diseases
Genetic/hereditary disorders
Rare
Autoimmune pancreatitis
Anatomic pancreaticobiliary abnormalities

Etiology

The disorders associated with pancreatitis fall into several broad categories (Table 1). The prevalence of different causes varies greatly among studies of acute pancreatitis in childhood. The variation likely results from the inherent limitations of retrospective studies, the bias or experience of the clinicians caring for children who have pancreatitis, incomplete investigations for causes, the greater number of patients recognized to have pancreatitis, and the recognition of new etiologies in childhood.

BILIARY DISEASE. Gallstone pancreatitis is a more common cause of acute pancreatitis in children than previously believed. Gallstone pancreatitis or other biliary disease should be suspected if the patient has elevations in transaminase levels and/or hyperbilirubinemia.

SYSTEMIC ILLNESS. In recent studies, acute pancreatitis associated with systemic illnesses accounted for more than 20% of reported cases. Typically, these children were in an intensive care unit. Pertinent associations include sepsis, shock (alone or with sepsis), hemolytic uremic syndrome, and systemic lupus erythematosus. Of these diseases, hemolytic uremic syndrome has had the highest prevalence. (3)(4) The

pathophysiologic mechanism is uncertain, although it is likely multifactorial. Inflammatory bowel disease can cause pancreatitis due to periampullary obstructive small intestinal disease, cholelithiasis, associated primary sclerosing cholangitis, and the effects of immunomodulating medications (mesalamine and 6-mercaptopurine). It is not unusual for infectious symptoms to be temporally associated with the onset of acute pancreatitis. With a few exceptions, such as the mumps virus, few viruses clearly cause acute pancreatitis. (3)

MEDICATIONS. A variety of medications increase the risk for pancreatitis. Commonly reported associations implicate L-asparaginase, valproic acid, azathioprine, mercaptopurine, and mesalamine as triggers of pancreatitis. (3) The mechanism behind medication-associated pancreatitis is unclear. In susceptible patients, the medication or its metabolites likely disrupt acinar cell metabolism.

TRAUMA. Although the prevalence of pancreatitis associated with trauma is probably not as high as previously thought, trauma remains an important cause of pancreatitis. Most often, unintentional blunt trauma causes damage to the pancreas, but child abuse can result in traumatic pancreatitis as well. (5)

IDIOPATHIC. Despite improvements in diagnostic testing, the rate of idiopathic pancreatitis continues to be significant and unchanged. (3)(4)

METABOLIC. Although metabolic diseases are uncommon causes of acute pancreatitis, it is important to recognize them because treatment can prevent recurrent episodes. Disorders that cause hypercalcemia, hypertriglyceridemia, and inborn errors of metabolism have all been associated with acute pancreatitis.

GENETIC/HEREDITARY. The common genetic mutations associated with pancreatitis generally cause ARP or CP and are discussed in the following text.

AUTOIMMUNE PANCREATITIS. Autoimmune pancreatitis has become increasingly recognized in childhood. Autoimmune pancreatitis occurs in two forms (types 1 and 2). Type 2 seems to be more common in children and has an association with inflammatory bowel disease and other autoimmune diseases. In adults, the diagnosis of type 1 autoimmune pancreatitis relies on elevated levels of immunoglobulin G4 (IgG4), diffuse or segmental enlargement of the pancreas, strictures of the pancreatic duct, and histologic features. In children, IgG4 elevation may not be present, even with typical histology. In general, and regardless of serum IgG4 status, pediatric (and adult) patients with type 1 or type 2 autoimmune pancreatitis respond to corticosteroid therapy. (6)

ANATOMIC PANCREATOBILIARY ABNORMALITIES. Pancreaticobiliary abnormalities such as pancreas divisum (Fig 2), abnormal junction of the common bile duct and main pancreatic duct (common channel syndrome), choledochal cysts, and annular pancreas increase the risk for acute pancreatitis. Pancreas divisum is present in up to 15% of the population. This anatomic abnormality occurs when the dorsal and ventral anlage of the pancreas fuse incompletely, leading to lack of communication between the dorsal (Santorini) and ventral (Wirsung) pancreatic ducts. Despite its proposed obstructive mechanism leading to acute pancreatitis, clinical causality is still controversial. Recent studies suggest that the presence of a *SPINK-1* (serine protease inhibitor Kazal type 1) or *CFTR* (cystic fibrosis transmembrane conductance receptor) mutation along with pancreas divisum increases the risk of acute pancreatitis and accounts for the observation that only a fraction of people who have pancreas divisum develop acute pancreatitis. (7)

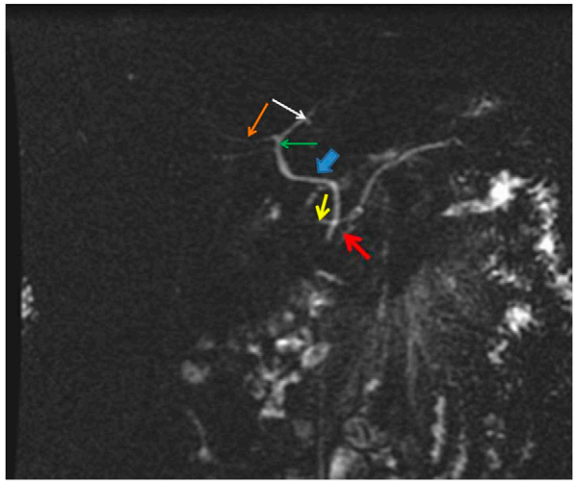

Figure 2. Magnetic resonance cholangiopancreatography showing pancreas divisum. Dorsal (yellow arrow) and ventral (red arrow) pancreatic ducts with separate insertion of dorsal pancreatic duct into minor papillae. The rest of the biliary tree is delineated: common bile duct (blue arrow), common hepatic duct (green arrow), right hepatic duct (white arrow), and left hepatic duct (orange arrow). Courtesy: William M. Peterson II, MD, and Sameh Tadros, MD, MSc, Department of Radiology; Children's Hospital of Pittsburgh of UPMC.

Diagnosis

Acute pancreatitis can occur in mild and severe forms. Although the definition of the two forms can vary depending on the author, in general, mild pancreatitis is limited to the pancreas and the peripancreatic fat, whereas severe disease includes pancreatic necrosis, involvement of other organs, cardiovascular collapse, infection, or fluid collections. Most children (≥90%) have mild disease. (5)

Acute pancreatitis in pediatric patients requires at least two of three criteria: (1) abdominal pain suggestive of or compatible with acute pancreatitis (ie, abdominal pain of acute onset, especially in the epigastric region); (2) serum amylase or lipase activity at least three times greater than the upper limit of normal; and (3) imaging findings compatible with acute pancreatitis.

ABDOMINAL PAIN SUGGESTIVE OF OR COMPATIBLE WITH ACUTE PANCREATITIS.

Abdominal pain has a frequency of 80% to 95% in pediatric patients who have acute pancreatitis. Specifically, pancreatitis has been shown to present with epigastric pain in 62% to 89% of patients and diffusely in 12% to 20% of patients. The classic presentation of epigastric pain radiating to the back occurs in only 1.6% to 5.6% of patients. Epigastric pain plus back pain is present in fewer than 10% of patients. (3) Assessing pain in children who are nonverbal, have static encephalopathy, or are developmentally delayed can be challenging. Parental report of irritability is a common presenting sign in nonverbal children. In infants and toddlers, abdominal distension, vomiting, and fever were common presenting complaints. (8)

SERUM AMYLASE OR LIPASE ACTIVITY AT LEAST THREE TIMES GREATER THAN THE UPPER LIMIT OF NORMAL.

Amylase and lipase values rise 2 to 12 hours and 4 to 8 hours, respectively, after the onset of pancreatic inflammation. It is important to note that the upper reference values of serum amylase and lipase vary among different laboratories; hence, reference values should always be given when considering levels. At present, both amylase and lipase should be measured because only one or the other may be elevated in individual patients, even in the presence of radiographic evidence for pancreatitis. It is important to note that other diseases can cause elevations of amylase and lipase (Table 2).

IMAGING FINDINGS COMPATIBLE WITH ACUTE PANCREATITIS.

The utility and timing of radiographic studies in children who have suspected acute pancreatitis remain controversial (Table 3). The frequency of gallstone pancreatitis in children provides the most compelling argument for early imaging. Endoscopic ultrasonography (EUS) and magnetic resonance cholangiopancreatography (MRCP) identify cholelithiasis best. (9)(10) MRCP is magnetic resonance imaging of the biliary tree and surrounding structures (pancreas and liver). Because fluid in the pancreaticobiliary ducts appears bright, they can be visualized easily. Although MRCP is expensive and requires general anesthesia in younger children, it has largely supplanted endoscopic retrograde cholangiopancreatography (ERCP) as the preferred diagnostic study for biliary and pancreatic ductal disease because it is less invasive and does not cause pancreatitis, which can occur after ERCP.

EUS is not widely available in pediatric centers. Transabdominal ultrasonography represents a reasonable compromise for evaluating patients who have suspected gallstone disease. Ultrasonography also may provide corroboration of acute pancreatitis and assist in identifying causes. Findings can include pancreatic edema, dilated main pancreatic duct, pancreatic calcifications, and fluid collections.

Contrast-enhanced computed tomography (CT) of the abdomen is a second option for imaging the pancreas. A CT scan can show the same findings as ultrasonography and also may provide information about the presence or absence of pancreatic necrosis. In general, CT scans are most useful several days into the course of acute pancreatitis if the patient fails to improve or if the pancreas is inadequately visualized on ultrasonography.

Management

The management of acute pancreatitis traditionally has consisted of pancreatic rest (no enteral feeding), antiemetics, analgesia, fluid support, and monitoring for complications. These treatments remain the mainstay of therapy, but the approach to pancreatic rest and fluid management has changed.

The initial treatment is directed at stabilizing the patient's condition. Limited adult data suggest that aggressive hydration in the first 24 hours decreases the risk of multiorgan system failure. (11) Thus, intravenous fluid boluses to rehydrate the patient and subsequent fluid administration at 1.5 times maintenance rates are recommended.

Antiemetics and analgesia are necessary to provide comfort and to avoid increased energy expenditure. Opioid analgesics in oral or parenteral forms usually are required for pain control in acute pancreatitis. There is no evidence to support the advantage of any particular medication. Despite the long-time teaching that morphine should be avoided because it may cause paradoxical contraction of the sphincter of Oddi, this effect has

Table 2. Pediatric Conditions Associated With Elevation of Amylase or Lipase Levels

Condition	Amylase	Lipase
Abdominal	• Acute pancreatitis • Biliary tract disease • Intestinal obstruction/ischemia • Mesenteric infarction • Peptic ulcer • Appendicitis • Ruptured ectopic pregnancy • Ovarian neoplasm	• Nonpancreatic abdominal pain • Acute cholecystitis • Esophagitis • Intestinal obstruction/ischemia • Peptic ulcer
Salivary gland	• Trauma • Infection (ie, mumps) • Sialolithiasis • Irradiation	
Thoracic	• Pneumonia • Pulmonary embolism • Myocardial infarction • Cardiopulmonary bypass	
Infectious	• Viral gastroenteritis • Pelvic inflammatory disease	• Human immunodeficiency virus infection
Metabolic	• Diabetic ketoacidosis • Pheochromocytoma	• Diabetic ketoacidosis • Hypertriglyceridemia
Neoplastic	• Ovarian, lung, esophageal, or thymic tumors	
Drugs	• Opiates	
Trauma	• Cerebral trauma • Burns	
Renal	• Renal insufficiency • Renal transplantation	• Renal insufficiency
Inflammatory	• Macroamylasemia • Celiac disease	• Macrolipasemia • Celiac disease
Miscellaneous	• Cystic fibrosis • Acute liver failure • Viral gastroenteritis • Pregnancy • Eating disorders: anorexia, bulimia	

not been demonstrated in clinical practice, and morphine can be used safely in patients who have acute pancreatitis. (12)

A careful directed investigation for treatable causes of acute pancreatitis should be conducted (Table 1). The routine use of antibiotics is not recommended; they should be reserved for patients who have evidence of infected necrosis.

Perhaps the greatest change in the management of acute pancreatitis is the early institution of nutrition. In patients who have mild acute pancreatitis, oral feedings can be started within 24 to 48 hours after admission. In the past, clear liquids were started, but recent studies in adults show that regular meals can be given. (13) Limited data suggest that the practice of prescribing a low-fat diet is not necessary. About 10% of patients will have abdominal pain after starting oral intake. Usually, feedings can be resumed in the patients in another 24 hours. (5) (14) An increase in serum levels of pancreatic enzymes is not an indication to stop feedings.

Patients who have severe pancreatitis also can be successfully fed early in the treatment course. Typically, these patients are fed through enteral tubes or by using total parenteral nutrition (TPN). Enteral feeding is preferred over TPN because of the complications associated with the intravenous catheter and the expense of TPN. The only clear indications for TPN include inability to tolerate enteral nutrition due to prolonged ileus, pancreatic fistulae, or complicating abdominal compartment syndrome.

The choice of enteral route, gastric or jejunal (which bypasses the ampulla of Vater), is controversial and generally depends on the custom at individual institutions. Both routes have been used successfully in adults who

Table 3. **Utility of Radiographic Imaging for Diagnosing Acute Pancreatitis**

Imaging	Comments
Abdominal ultrasonography	Advantages • Reasonable test to assess for gallstones • Short duration • No radiation exposure • Usually available any time of day Disadvantages • Operator dependence • Potential for bowel gas to obscure pancreas
Abdominal computed tomography	Advantages • Better than ultrasonography for detecting changes associated with pancreatitis • Short duration • Usually available any time of day • Utility lies in detecting pancreatic necrosis if suspected Disadvantages • Rather low sensitivity for detecting changes associated with acute pancreatitis • Radiation exposure • Cannot visualize gallstones
Magnetic resonance cholangiopancreatography	Advantages • Good assessment of pancreatic parenchyma, ducts, and gallstones Disadvantages • May not be available 24 hours a day • Limited in acutely ill patients due to procedure time • Duration of test may necessitate sedation in younger children

have severe acute pancreatitis. The choice of formula, elemental or polymeric, is also a matter of local practice. Direct comparisons of elemental and polymeric formulas have failed to demonstrate differences in feeding tolerance, morbidity, or mortality between the formulas. (15)

Complications

Table 4 details the potential local and systemic complications of acute pancreatitis in pediatric patients. These complications also can be classified by early versus late onset. Pancreatic fluid collections are the most common complication of acute pancreatitis in pediatrics and usually are caused by necrosis or trauma. Pseudocysts (Fig 3) are defined as a homogeneous collection of pancreatic fluid encased by a membrane of granulation tissue. It takes approximately 30 days for the granulation tissue to develop, although any fluid collection is called a pseudocyst. Pseudocysts and other fluid collections typically resolve despite the initial size but occasionally may require drainage, which can be conducted by using interventional radiology, endoscopy, or surgery. Death is uncommon in pediatric patients who have pancreatitis, and most reported deaths occur in patients who have other significant disease, such as trauma or sepsis. (3)(5)

Outcomes in acute pancreatitis are similar among pediatric age groups, are better than in adults, and are not correlated with initial amylase and lipase levels. There are no existing scoring systems similar to the APACHE (Acute Physiology and Chronic Health Evaluation) or the Ranson system used in adults that can accurately predict outcome in pediatrics. (4)

Acute Recurrent Pancreatitis

ARP is defined as at least two episodes of acute pancreatitis per year, or more than three episodes over a lifetime, in a patient without CP or a pancreatic pseudocyst. Reliable estimates of the risk of recurrence are not available in pediatric patients. Case series report that 10% to 35% of patients will have recurrence. (3) The pathophysiology of recurrent episodes likely parallels the same pathways that are present in patients who experience a single episode, although these patients may have additional genetic modifiers that increase the likelihood of developing acute pancreatitis, given a particular trigger.

Etiology

As in patients who experience a single episode of pancreatitis, many patients who have ARP have no identifiable cause for their illness. Table 5 lists common etiologies associated with ARP. Many of the causes discussed here can lead to recurrent episodes of pancreatitis, including biliary disease, anatomic pancreaticobiliary abnormalities, inflammatory bowel disease, and autoimmune pancreatitis.

Table 4. Complications of Acute Pancreatitis

Local
- Inflammation
  - Localized to pancreas
  - Systemic extension
- Ileus
- Pancreatic edema
- Pancreatic necrosis
- Pancreatic abscess
- Fat necrosis pancreatic hemorrhage
- Pancreatic pseudocyst
- Pancreatic duct rupture
- Pancreatic duct stricture
- Thrombosis of adjacent blood vessels

Systemic
- Shock
- Sepsis
- Hypermetabolic state
- Hypocalcemia
- Hyperglycemia
- Vascular leak syndrome
- Multiorgan system failure
- Disseminated intravascular coagulation
- Pleural effusions
- Acute renal failure
- Splenic artery pseudoaneurysm

Other causes to consider after a second, distinct episode of pancreatitis are discussed in the following text.

GENETIC MUTATIONS ASSOCIATED WITH PANCREATITIS. In the last 15 years, mutations in several genes have been associated with increased risk for pancreatitis. (16)(17)

PRSS-1. Several mutations in the *PRSS-1* gene that encodes cationic trypsinogen cause hereditary pancreatitis. Inheritance is autosomal dominant with an 80% penetrance. The mechanism by which mutations in *PRSS-1* lead to pancreatitis remains under investigation. Prevailing theories are increased autoactivation of trypsinogen (an inactive form stored in the acinar cell) to trypsin or increased resistance to inactivation of trypsin within the acinar cell. Patients present in childhood with ARP and later progress to CP with a high likelihood of exocrine and endocrine deficiency. The lifetime risk of pancreatic cancer is 40% or greater in these patients. (16)(17)

SPINK-1. The gene product of SPINK-1 is produced in acinar cells and acts as a defense for premature tryspinogen activation. Several mutations in *SPINK-1* increase susceptibility to ARP and CP. Patients who have homozygous or compound heterozygous mutations have a higher risk than patients who have heterozygous mutations. *SPINK-1* mutations are considered disease modifiers because most people who have these mutations, even when homozygous, do not develop acute pancreatitis, ARP, or CP. The mechanism of increased risk associated with *SPINK-1* mutations is thought to be related to decreased ability to inactivate trypsin. Definitive evidence for this mechanism is not available and other mechanisms, such as toxicity from misfolded protein, remain possible. (16)(17)

CFTR. As with *SPINK-1* mutations, *CFTR* mutations are considered disease modifiers. Heterozygous, compound heterozygous, and homozygous mutations increase the risk for ARP and CP. The increased risk is less for

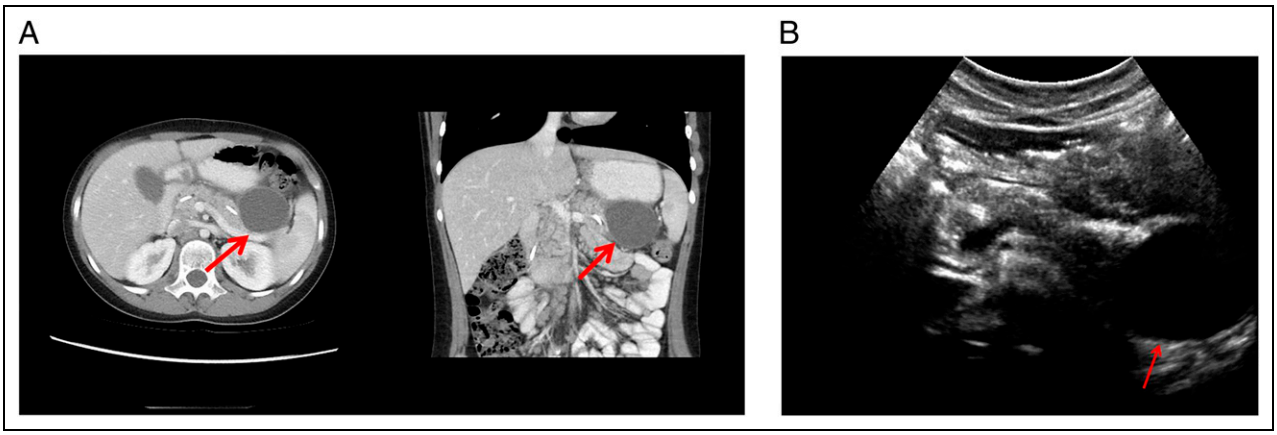

Figure 3. Scans of pancreatic pseudocyst (arrow). A. Computed tomography. B. Ultrasonography. Courtesy: William M. Peterson II, MD, and Sameh Tadros, MD, MSc, Department of Radiology; Children's Hospital of Pittsburgh of UPMC.

Table 5. Causes of Acute Recurrent and Chronic Pancreatitis

- Biliary calculi
  - Macrolithiasis
  - Microlithiasis (<2 mm)[a]
  - Sludge[a]
- Congenital pancreaticobiliary abnormalities
  - Anomalous pancreaticobiliary junction
  - Choledochal cyst
  - Annular pancreas
  - Pancreas divisum[b]
- Genetic[c]
  - Hereditary pancreatitis, *PRSS-1* mutation
  - *SPINK-1* mutation[b]
  - *CFTR* mutation
- Duodenal inflammation
  - Crohn disease
  - Celiac disease
  - Infection
- Medications
- Sphincter of Oddi dysfunction
- Metabolic
  - Hypercalcemia
  - Hypertriglyceridemia
- Intestinal duplication cyst
  - Gastric
  - Duodenal
- Autoimmune
  - Localized to pancreas
  - Systemic disorder
- Idiopathic[c]

CFTR=cystic fibrosis transmembrane conductance regulator; *PRSS-1*=cationic trypsinogen; *SPINK-1*=serine protease inhibitor Kazal type 1.
[a]Controversial associations.
[b]Only causative if present with another predisposing factor (eg, *CFTR* heterozygote mutation).
[c]Most common causes of chronic pancreatitis in pediatric patients.

patients who have heterozygous mutations than it is for patients with two affected alleles. In general, one or both affected alleles results in a *CFTR* protein with some function. These patients lack other clinical features of cystic fibrosis or have mild disease in other organs and are pancreatic-sufficient at presentation, although some will develop pancreatic insufficiency over time. When interpreting results of a genetic screen of the *CFTR* gene, it is important to remember that the effect of many changes in the gene sequence on protein function is unknown. (16)(17)

CTRC. The chymotrypsin C gene (*CTRC*) encodes for the digestive enzyme chymotrypsin C. There are increased rates of *CTRC* mutations in patients who have ARP and CP. The mutations are disease modifiers. Because *CTRC* can inactivate trypsin in vitro, it has been suggested that this gene acts to protect acinar cells from inappropriate trypsinogen activation. (16)(17)

DRUG-INDUCED PANCREATITIS. A careful review of any medications and home remedies used by the patient should be conducted, and any medications associated with pancreatitis should be discontinued.

SPHINCTER OF ODDI DYSFUNCTION. The role of sphincter of Oddi dysfunction in causing ARP in children is unclear. No studies have suggested that sphincterotomy (cutting the muscles around the sphincter) has any efficacy in treating children with ARP.

METABOLIC. The metabolic causes for ARP (hypercalcemia, hypertriglyceridemia, and inborn errors of metabolism) have not been studied extensively but may be rare triggers for ARP.

DUPLICATION CYSTS. Duplication cysts of the duodenum or stomach should be considered; these lesions may lead to ARP secondary to pancreaticobiliary obstruction, based on their location. They can be difficult to detect and may be apparent only after multiple investigations with different imaging modalities. It is important to note that duodenal duplication cysts can oppose the head of the pancreas closely and be interpreted as a pseudocyst.

Diagnosis and Management

The diagnostic criteria for each ARP episode and its treatment are the same as described earlier for acute pancreatitis. It is important to thoroughly explore all potential causes and triggers because many are preventable and knowledge of the cause can guide management and prognosis.

In cases of ARP, genetic screening for *PRSS-1* and *SPINK-1* mutations should be conducted. Although complete gene sequencing of *CFTR* is available, this investigation is not necessary for all patients. A sweat test should be performed. Patients who have mild/variable *CFTR* mutations will have values in the indeterminate or low positive zones. The presence of a *CFTR* mutation can then be confirmed by using complete gene sequencing. Patients who have *CFTR* mutations should be referred to a CF center for additional evaluation.

The anatomy of the biliary and pancreatic ducts should be determined by using MRCP. This study also can identify annular pancreas or congenital pancreatic cysts. Select patients may require ERCP to confirm and

possibly treat ductal anomalies. For instance, pancreas divisum is treated by using sphincterotomy and stenting of the minor papilla. Additional evaluation for systemic inflammatory disease, especially for Crohn disease, should be considered. Upper endoscopy can identify inflammatory or mass lesions that may partially obstruct the ampulla. Autoimmune pancreatitis may be suggested by results of the MRCP. IgG4 should be measured although its utility in identifying children who have autoimmune pancreatitis has been questioned. Imaging studies, usually ultrasonography or CT scan, will identify duplication cysts. Because current opinion holds that ARP progresses to CP, effective management has the potential to stop this progression.

Chronic Pancreatitis

Definition

CP is defined as a process leading to irreversible destruction of the pancreatic parenchyma and ducts and loss of exocrine function. Many of these patients have a history of ARP before the irreversible changes in pancreatic anatomy and function become apparent. (18)

Epidemiology

CP can present at all ages in children. Classic cystic fibrosis is the most common cause in children and will not be discussed further in this review. The incidence and prevalence of CP in childhood are not known.

Etiology

The causes of CP are the same as those of ARP (Table 5). In children, CP is usually idiopathic or associated with mutations in *PRSS-1*, *SPINK-1*, *CFTR,* or *CTRC* genes, alone or in combination.

Pathophysiology

CP results from the sequelae of long-standing destructive inflammation. Current theory suggests that CP begins with acute pancreatitis and progresses to fibrosis. Instead of resolution, as in acute pancreatitis, the destructive process continues in susceptible individuals. Susceptibility and rate of progression are likely influenced by genetic and environmental modifiers. (18)

Diagnosis

The diagnosis of CP is clinical and based on a combination of symptoms, imaging studies, and functional insufficiency. It is important to consider all of these parameters when CP is suspected in a patient, because diagnosis often is delayed. With advanced disease, amylase and lipase levels will not be elevated, even in the presence of disabling pain.

CLINICAL FEATURES. For many patients, recurrent episodes of pancreatitis will raise concerns about CP. Patients present with mild to intense abdominal pain, usually epigastric. The pain can be constant or intermittent and often is described as deep and penetrating, with radiation to the back. Many times the pain is episodic, as in ARP. There are numerous causes of this pain. The pain can result from obstruction of pancreatic ducts by fibrosis or stones, inflammation of the parenchyma (acute-on-CP), perineural inflammation, or pain imprinting in the peripheral or central nervous system. Rarely, patients present with symptoms of malabsorption, such as weight loss, fatty stools, or diarrhea. Even rarer are patients who present with jaundice from extrahepatic biliary obstruction caused by pancreatic fibrosis or a pseudocyst. An occasional patient will have an upper gastrointestinal hemorrhage from venous thrombosis as the presenting sign. Diabetes develops late in the course of CP, and children seldom, if ever, present with symptoms of diabetes.

IMAGING. Imaging studies provide evidence of morphologic change in the gland or ducts. Transabdominal ultrasonography, CT, MRCP, ERCP, and EUS each can provide evidence of chronic change in the pancreas. Currently, MRCP is the imaging method of choice. This modality has limitations in that the side branches of the main pancreatic duct are not well defined. ERCP is better at defining ductal anatomy but usually is not required. CT can reliably detect calcification, gland atrophy, fat replacement, and ductal dilation but is not as sensitive for duct changes as MRCP or ERCP. In adults, EUS has gained acceptance for detecting changes in CP, although there is disagreement about the standards for diagnosing chronic changes by using this method.

PANCREATIC FUNCTION TESTING. Pancreatic function testing can identify pancreatic insufficiency and support the diagnosis of CP. Duodenal intubation with secretin-cholecystokinin stimulation remains the reference standard for diagnostic testing, but this option is not widely available. More commonly, pancreatic secretions are collected at upper endoscopy. This approach likely underestimates pancreatic secretion, leading to the incorrect diagnosis of pancreatic insufficiency in some patients. In recent years, fecal elastase has been used to screen for pancreatic insufficiency. This test is widely available, easy to conduct, and can be performed even if patients are taking pancreatic enzyme supplements. Like all indirect tests, fecal elastase has poor sensitivity for detecting mild to moderate pancreatic insufficiency. Lastly, watery stools dilute the fecal elastase concentration, and false-positive findings can occur. The 72-hour

fecal fat collection remains the best test for steatorrhea. As with other noninvasive tests, the 72-hour fecal fat collection result is abnormal only with advanced disease. Fat testing should not be used alone for diagnosis because disease of the intestinal mucosa can cause steatorrhea.

Management

The stage and etiology of CP determine its management. When recurrent episodes of acute pancreatitis dominate the clinical course, the management is identical to that of acute pancreatitis. With disease progression, chronic pain management and therapy for pancreatic insufficiency are required. In a few pediatric patients, diabetes will require treatment.

Because unrelenting pain affects many patients, most of the therapeutic effort centers on pain control. At first, acetaminophen may be effective, but therapy generally advances to narcotics. Other approaches to pain control are used, but none has clear efficacy. Pancreatic enzyme supplements and antioxidant therapy (selenium, ascorbic acid, β-carotene, α-tocopherol, and methionine) are prescribed frequently as therapeutic trials.

Endoscopic treatment for CP should be considered only when ductal strictures or pancreatic duct stones are present or for symptomatic pseudocysts. The role of endoscopic sphincterotomy and stent placement remains controversial. Surgical approaches are still used in select patients. Localized disease can be treated with partial pancreatic resection.

Total pancreatectomy with islet cell autotransplant is currently offered to patients who have genetic causes of pancreatitis and to those afflicted with unrelenting pain. Although many patients have pain relief, a number of patients continue to have pain. In up to 20% of adults, the pain is as intense as it was before the resection. One third of these patients have no insulin requirement; another one third will require low doses of insulin; and the remaining one third will develop brittle diabetes. Preadolescents are more likely to be insulin-independent than are older children and adults. Because islet cell yield is the best predictor of diabetes outcome and the yield decreases in more severe disease, timing of the operation is important. Unfortunately, no guidelines exist to direct decision-making. (19)(20)

Pancreatic insufficiency is treated with pancreatic enzyme replacement therapy. The goal is to restore digestive function and maintain weight gain and growth. Because no studies of the effective dose range exist for patients who have pancreatitis, the recommendations for treating patients who have cystic fibrosis are used for enzyme dosing in patients who have CP.

Complications

Long-term natural history studies are beginning to delineate the prognosis of CP. Contrary to previous teaching, the pain of CP does not "burn out." The pain may vacillate in intensity and frequency, but it will not resolve with time. Both pancreatic insufficiency and diabetes appear later in the course. Diabetes may take 2 or 3 decades to become clinically significant. Even so, pediatric patients will likely develop diabetes in their lifetime. Pancreatic cancer is a long-term risk for all pediatric patients who have CP. In hereditary pancreatitis, pancreatic cancer appears first in the fourth decade (incidence of 0.5%), and the incidence increases with age. (21) The high probability of pancreatic cancer is a factor in deciding whether to proceed with total pancreatectomy and islet cell autotransplant.

Summary

- The prevalence of acute pancreatitis is increasing in pediatrics (based on strong research evidence). (1)
- There are etiologic differences between pediatric and adult patients who develop acute pancreatitis, with a notable rate of idiopathic cases (based on strong research evidence). (3)(4)
- An elevated amylase or lipase level in the absence of clinical symptoms or radiologic findings is not diagnostic of pancreatitis, although pediatric patients who have pancreatitis may have a wide variety of presenting clinical symptoms (based on strong research evidence). (3)(8)
- Normal values of amylase and lipase differ among laboratories.
- Successful early feeding is possible in treating acute pancreatitis and may not necessitate a low-fat diet or bypass of the ampulla of Vater (based on some research evidence as well as consensus). (5)(15)
- Chronic pancreatitis is a specific diagnosis characterized by irreversible pancreatic changes and can be diagnosed only via radiologic and biochemical evidence, in addition to clinical symptoms (based on strong research evidence). (16)

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PIR Quiz

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1. Which of the following scenarios clearly defines a patient with acute pancreatitis?
   - A. Amylase level two times the upper limit of normal, lipase level two times the upper limit of normal, mid-epigastric pain, and normal pancreas on abdominal ultrasonography.
   - B. Elevated lipase level, no symptoms, and pancreatic inflammation on abdominal computed tomography (CT).
   - C. Amylase level four times the upper limit of normal, lipase level two times the upper limit of normal, mid-epigastric pain, and normal pancreas on abdominal ultrasonography.
   - D. Amylase level two times the upper limit of normal, lipase level 1.5 times the upper limit of normal, no symptoms, and normal pancreas on abdominal CT.
   - E. Amylase level 1.5 times the upper limit of normal, lipase level two times the upper limit of normal, no symptoms, and normal pancreas on abdominal CT.

2. A 10-year-old girl has acute pancreatitis. She was hospitalized yesterday and has been given intravenous fluids for 24 hours. The girl is feeling better, and her mother would like to know when the girl can begin eating again. You are most likely to respond that:
   A. She can begin eating after 24 hours with no pain.
   B. She can eat when her lipase levels have normalized.
   C. She should be able to start eating within the next 24 hours.
   D. You will order parenteral nutrition before she eats by mouth.
   E. You will request nasojejunal tube feedings today.

3. A 16-year-old girl has chronic pancreatitis associated with the cationic trypsinogen (*PRSS-1*) gene mutation. She takes narcotic medications to control her abdominal pain and supplements, including pancreatic enzyme supplements, selenium, and ascorbic acid. Her blood glucose and hemoglobin A1c levels are normal. She has read that she is at increased risk for pancreatic cancer. You are most likely to respond that she:
   A. Has a small (<10%) lifetime risk of developing pancreatic cancer.
   B. Has decreased risk related because of her adequate insulin production.
   C. Is at small risk for developing pancreatic cancer in her 30s.
   D. Is at the same risk as the general population.
   E. Is only at risk if she has a homozygous gene mutation.

4. A 7-year-old boy has had three episodes of acute pancreatitis. This boy's father and paternal grandmother also have a history of recurrent pancreatitis. The boy's grandmother had pancreatic cancer and is deceased. The boy's father takes pain medication daily for chronic pancreatitis. On further testing, the most likely study to elucidate the etiology of this boy's pancreatitis is:
   A. Cystic fibrosis transmembrane conductance regulator mutation testing.
   B. Endoscopic retrograde cholangiopancreatography.
   C. Magnetic resonance cholangiopancreatography.
   D. *PRSS-1* mutation testing.
   E. Serine protease inhibitor Kazal type 1 mutation testing.

5. A 21-year-old man with chronic pancreatitis is in severe pain. He has a *PRSS-1* mutation, and his father has pancreatic cancer. He would like information about surgical treatment. You are most like to tell him that:
   A. He should undergo endoscopic sphincterotomy before considering pancreatectomy.
   B. His life-time risk for diabetes is much higher with the surgery.
   C. His risk for diabetes after pancreatectomy is related to islet cell yield with the procedure.
   D. Pancreatic enzyme function is preserved after pancreatectomy.
   E. The pain from his pancreatitis will resolve after pancreatectomy.

Pediatric Pancreatitis

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