

A Review on Acute Pediatric Pancreatitis

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Abstract

Nowadays, acute pancreatitis is not a rare disease in children and adolescences and the incidence of the disease has increased in pediatric patients over the past two decades. Acute pancreatitis in children can be triggered by a wide array of factors such as drugs, infections, trauma, anatomic anomalies and metabolic disorders. The signs and symptoms of acute pancreatitis are non-specific with an age-related pattern. The most common symptoms are upper abdominal pain and vomiting. Other less common signs and symptoms include abdominal discomfort, tachycardia, fever, and hypotension, jaundice and back pain. Since the signs and symptoms of acute pancreatitis are non-specific, it should be considered during the differential diagnosis of abdominal pain in children and needs prompt treatment because it may become a life-threatening disorder. Diagnosis of acute pancreatitis is principally achieved by meeting two of the following criteria: compatible clinical symptoms including abdominal pain, nausea, vomiting, or back pain; > 3 fold increase in serum amylase and/or lipase; presence of radiographic evidence including pancreatic edema on ultrasound or computed tomography. To provide a framework to review the diagnosis in pediatrics and identify evidence-based guidelines to manage acute pancreatitis in children, the current concepts on the diagnosis and treatment of pediatric acute pancreatitis are summarized.

Keywords: Acute Pediatric Pancreatitis, Diagnosis, Treatment

1. Context

Acute pancreatitis is an emerging problem in pediatrics, and its incidence has increased over the past two decades. In addition, increasing the awareness of physician likely accounts for the increase in the diagnosis of acute pancreatitis in children and adolescences (1, 2). The etiology of acute pancreatitis in children differs from that of adults. Biliary disease, metabolic, hereditary, and anatomic anomalies and trauma are the more prominent causes of acute pancreatitis identified in children (2-5). Abdominal blunt trauma and viral infections are also common causes of acute pancreatitis in children (1, 2). The diagnosis of acute pancreatitis requires two of the three following criteria: 1) Biochemical tests including serum amylase or lipase above three times the upper reference limit, 2) Appropriate clinical findings, and 3) Radiologic evidence of acute pancreatitis (1, 2, 6, 7). Besides peritoneal irritation, and other typical findings in physical examination of patients with acute pancreatitis, the exocrine secretory function may dispute the emphasis on the importance of early diagnosis of the disease (8, 9). Acute pancreatitis is also a reversible process with no permanent effects on the pancreatic parenchyma or function. However, it may be life-threatening if it is severe or remained untreated

(2, 5-10). Abdominal pain is an important early symptom in children (11, 12). The frequency of abdominal pain in older children, as a first symptom was similar to that of the adults, whereas in younger children, vomiting was reported as an important clinical symptom (13). The characteristics, location and triggers of abdominal pain, in addition to physical examination of the abdomen, are important clues in the diagnosis of acute pancreatitis. Jaundice, fever, diarrhea, back pain, irritability and lethargy may be other symptoms. Presence of jaundice and clay-colored stools suggest a biliary system abnormality such as a choledochal cyst and there may be a palpable abdominal mass (2). Infants and toddlers cannot explain abdominal pain, but vomiting, irritability and lethargy are common (12). In severe acute pancreatitis, shock may be the initial presentation in children, followed by symptoms of multi-organ failures such as dyspnea, oliguria, hemorrhage and mental status changes (14). Pancreatitis can occur in the first decade of life following viral infections such as mumps, Epstein-Bar virus and often spontaneously resolve within one week (2, 5, 7, 13-17). These symptoms are considered as general symptoms in children, but sometimes can be easily confused with signs of other underlying diseases. In cystic fibrosis, as an inherited cause of pancreatitis, the onset

of the disease is characterized by an acute constant, diffuse abdominal pain in right upper quadrant (RUQ) and occasionally to the left upper quadrant (LUQ) and can radiate to the back (18). Acute pancreatitis may be occasionally without pain (8, 9, 17, 19, 20). In cases with severe necrotizing pancreatitis (NP), associated with extensive irritation of peritoneum, shock, hypotension, flank ecchymosis (Grey-Turner sign) or periumbilical ecchymosis (Cullen sign) are more specific and are associated with poor prognosis. Fever, tachycardia, epigastric tenderness, shallow breathing (due to irritation of diaphragm) and dyspnea (caused by pleural effusion) are the other symptoms (2, 9, 15). Less common symptoms of necrotizing pancreatitis are subcutaneous fat necrosis (panniculitis), thrombophlebitis, polyarthrititis and abdominal mass (pancreatic pseudocyst) (9, 21). The study summarized the current concepts on the diagnosis and treatment of pediatric acute pancreatitis to provide a framework to review the diagnosis in pediatrics and identify evidence-based guidelines to manage acute pancreatitis in children.

2. Evidence Acquisition

The current narrative review was performed on databases of PubMed in MEDLINE area and Google scholar about pediatric acute pancreatitis. Articles not related to pediatrics population were excluded. The concepts of diagnosis and treatment aspects of the disease were extracted from the reviewed articles and the qualitative results are reported here.

3. Results

3.1. Laboratory Tests

Elevated pancreatic enzymes in serum and/or urine, and non-enzymatic pancreatic secretions are associated with acute pancreatitis.

Pancreatic enzymes: At the first phase of the disease, pancreatic enzymes rise and in the next phase pancreatic secretions are ceased due to pancreatic duct obstruction. Rising of pancreatic enzymes are not limited to pancreatitis and can be observed in other disorders. Measurements of serum lipase from the first to third day of an attack of acute pancreatitis are more specific than measuring the serum amylase (2, 9, 15). Serum amylase with 10 hours half-life rises within the first 6 - 12 hours of the onset of the disease. This is a non-specific finding and in non-complicated cases, it remains elevated for three to five days. Serum amylase is usually elevated three folds more than normal level and in some cases with underline hyperlipidemia, serum amylase level is not very high. Serum lipase has a sensitivity of 86.5% -100% and specificity of 84.7%

- 99.0% for diagnosis of acute pancreatitis and its sensitivity is higher compared to serum amylase. Serum lipase levels seven times higher than normal are reported in severe pancreatitis, within 24 hours after onset of the disease (22, 23). The degree of elevation and serial changes, however, are generally not correlated with disease severity (24). Other biochemical findings are isoamylase, chololipase, carboxyl ester lipase phospholipase, carboxypepsidase, trypsin and trypsinogen II. Non-enzymatic pancreatic secretion can point to trypsinogen activating peptide. Inflammatory factors including blood level of polymorphonuclear leukocytes (PMN), tumor necrosis factor (TNF), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are elevated at different degrees in pancreatitis. There are some changes in pancreas secondary to inflammation such as soap bubble phenomenon (necrotizing inflammation) including hypocalcemia, hyperlipidemia and hyperglycemia (17, 25, 26).

As already mentioned, the pancreas and salivary gland are two main sources of serum amylase, and its increase is neither specific in pancreatitis nor explains the severity of inflammation. Table 1 shows the most common causes of hyperamylasemia and their origins (2, 16, 25, 27).

3.2. Radiologic Findings

3.2.1. Plain Radiography of Abdomen

There is no specific finding in acute pancreatitis. The findings vary from normal to mild ileus, sentinel loop and transfer colon dilatation. Therefore, normal plain abdominal radiography cannot rule out pancreatitis.

3.2.2. Abdominal Ultrasonography

Inflammation and enlargement of pancreas can be identified by ultrasonography. In some circumstances, cholelithiasis can be recognized. Biliary tree assessment is possible by this technique, but necrosis is not identified. Presence of calcification in chronic inflammation can be easily identified by ultrasonography.

3.2.3. Pancreas CT and MRI

Abdominal computed tomography (CT) with oral contrast is the best imaging technique used to diagnose pancreatitis and observation of its severity and complications and assessment of renal secretion phase. Swelling of pancreas, necrosis and pre- pancreatitis inflammation, acute accumulation of fluid caused by cyst, abscess, interpancreatic or pre-pancreatic hemorrhage (2, 15, 16, 26, 27).

As mentioned before, there are several underlying causes for acute pancreatitis. Identification of these causative factors is essential in the treatment of the disease. Table 2 lists a number of underlying causes of acute

Table 1. Most Common Causes of Hyperamylasemia and Their Origins

Disease	Dominant Iso-Form of Amylase
Pancreatic disease	
Acute and chronic pancreatitis, post ERCP, pseudocyst, pancreatic ascites	P
Acute cholecystitis	P
Intestinal disease	P
Parotitis	P
Trauma	P
Surgery	P
Cholecystitis	P
Obstruction	P
Radiation	P
Infarction	P
Salpingitis, EP perforation	S
Anorexia nervosa	S/P
cirrhosis	S/P
Malignancies	S
Acidosis and ketoacidosis	S/P
Pancreatic insufficiency	S/P
Macroamylasemia (without amylasuria)	Macroamylase
Fallopian tube disease	

Abbreviations: P, Pancreatic; S, salivary; ERCP, endoscopic retrograde cholangiopancreatography.

pancreatitis based on clinical manifestations and physical examination (8, 9, 15, 27).

American gastroenterology association (AGA) recommended the following guidelines in patients suspected to pancreatitis:

1. Measurements of serum amylase, lipase, triglyceride (TG), calcium, hepatic enzymes,
2. Abdominal sonography at first and necrosis at the phase of disease and remission,
3. Abdominal sonography or abdominal CT in non-recognized or suspected cases,
4. The most often invasive assessments are not necessary in the first episode cases and in patients less than 40 years old. In recurrent cases, endosonography and/ or endoscopic retrograde cholangiopancreatography (ERCP) should be done and genetic tests should be performed in specific cases (2, 16, 27).

3.3. Severity Index

To select appropriate initial treatment and predict the prognosis, rapid and precise assessment of severity index

Table 2. Underlying Causes of Acute Pancreatitis Based on Clinical Manifestations and Physical Examination

Clinical Features	Impression	Laboratory Testing
History of colic pain and/or cholangitis, hyperbilirubinemia and ALT	Cholelithiasis	EUS, MRCP, ERCP and Sonography
High risk group exposed to drugs	Drug related pancreatitis	Withdrawal
Family history of pancreatitis	Familial hyperlipidemia, chronic familial hyperlipidemia	Serum lipid concentration, genetic specific test
Presence of milky serum	Hyperlipidemia	Serum lipid concentration
History of trauma, abdominal surgery or ERCP	Trauma	Related to trauma or interventional approach
Hemorrhagic shock, abdominal vessels surgery, angiography	Vascular	Related to intervention or manipulation, other tissue involvement, biopsy, presence of eosinophil in urine
Frequent hypercalcemia attacks	Hypercalcemia	Increased Ca ²⁺
Hypertension, proteinuria, cutaneous lesion and neuropathy	PAN	Biopsy from muscle, skin or nerve, ANCA, and angiography
Idiopathic recurrent pancreatitis	Biliary microlithiasis, bifurcation pancreas, Oddi sphincter malfunction	ERCP and manometry, MRCP, with secretin

Abbreviations: ALT, alanine aminotransferase; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography; PAN, polyarteritis nodosa; ANCA, antineutrophil cytoplasmic antibodies.

is useful. In 2002, the first scoring system to predict the severity of childhood acute pancreatitis was introduced by DeBanto et al. (14). This modified system is composed of the following eight items: age (< 7 years old), weight (< 23 kg), white blood cell count at admission (> 18500 cells/ μ L), lactic dehydrogenase at admission (> 2000 U/L), 48-hour trough Ca²⁺ (< 8.3 mg/dL), 48-hour trough albumin (< 2.6 g/dL), 48-hour fluid sequestration (> 75 mL/kg per 48 hours), and 48-hour rise in blood urea nitrogen (> 5 mg/dL). They set the cut-off to predict a severe outcome at three criteria. This scoring system is not exact for Asian children and has limited ability to predict acute pancreatitis severity in children and adolescents in the United States (28, 29). Recently, a new severity assessment is reported to have used the modified acute pancreatitis severity scoring system of the ministry of health, Labour and Welfare of Japan (JPN score) in children (30, 31). The pediatric JPN scores included eight parameters as follows: (1) Base excess

≤ -3 mEq or shock (systolic blood pressure cutoffs according to the age group); (2) $\text{PaO}_2 \leq 60$ mmHg (room air) or respiratory failure; (3) Blood urea nitrogen ≥ 40 mg/dL [or creatinine (Cr) ≥ 2.0 mg/dL] or oliguria (< 0.5 mL/kg per hour); (4) Lactate dehydrogenase $\geq 2 \times$ the value of the upper limits; (5) Platelet count $\leq 1 \times 10^5/\text{mm}^3$; (6) Calcium ≤ 7.5 mg/dL; (7) C-reactive protein ≥ 15 mg/dL; (8) Number of positive measures in pediatric systemic inflammatory response syndrome (SIRS) score ≥ 3 ; and (9) Age < 7 years old or/and weight < 23 kg. The cut-off to predict a severe outcome was set at three criteria.

Recently, it was reported that the CT severity index was superior to a clinical scoring system to identify acute pancreatitis in children at risk to develop serious complications (32, 33).

3.4. Differential Diagnoses

3.4.1. Biliary Colic

In biliary colic, pain is constant and the duration of biliary colic is typically six to eight hours. Sometimes there is a known history of hepatic disorder and cholelithiasis. The disease can be associated with icter.

3.4.2. Visceral Perforation

Visceral perforation most often occurs following a trauma and perforation of bowel or biliary tracts. The symptoms of peritoneal irritation are vomiting, board-like abdomen and shock according to the underlying disease. The diagnosis of peritonitis is usually based on history, physical exam and other diagnostic modalities including plain radiography of the abdomen, sonography and abdominal CT-scan that can be helpful to diagnose the disease.

3.4.3. Peptic Ulcer

In peptic ulcer, the pain can be felt on epigastric or upper umbilical area similar to that of pancreatitis. Pain often has slow onset and recurrent nature. Previous history of peptic ulcer disease, hematochezia and melena, use of other diagnostic modalities such as endoscopy can be helpful for differential diagnosis.

3.4.4. Special Surgical Problems

Postoperative abdominal pain following ilioinguinal invagination duodenal hematoma, hemobilia, biliary tract obstruction and duodenal obstruction can mimic abdominal pain caused by pancreatitis (2, 8, 9, 15). Precise consideration to history and physical examination of the child, presence or absence of trauma history, cholangitis, gallstones and cholelithiasis, history of current surgery, use of diagnostic modalities such as abdominal sonography and abdominal CT scan can be helpful to differentiate the diseases.

3.5. Treatment

3.5.1. NPO

3.5.2. Treatment of Underlying Causes

a. ERCP to remove the obstruction caused by cholelithiasis (1)

b. Treatment of hypocalcaemia and withdrawal

3.5.3. Pain Relief

The analgesics used for pain management include pentazocine, metamizole, and morphine (34-36). In spite of concerns that morphine may cause sphincter of Oddi spasm and thus exacerbate AP, the limitations and controversies about the effect of morphine are significantly different from those of other opioids (37). The duration of meperidine is shorter than that of morphine and there is the risk of neurotoxic metabolites with repeated dosing. Direct comparison of meperidine and morphine in AP is missing. The μ -opioid antagonists such as methylnaltrexone (38) and alvimopan that improves opioid-induced dysmotility are not used routinely in pediatrics (39).

3.5.4. Fluid Therapy

Since fluid leaks into the surrounding tissue following inflammatory process associated with acute pancreatitis, adequate infusion to supplement extracellular fluid is needed during initial treatment (40).

3.5.5. Prevention of Infections

Infection is one of the most frequent side effects of pancreatic necrosis and is usually caused by intestinal bacteria. In severe cases, admission in the intensive care unit (ICU) and control of vital organs are necessary. In severe necrotizing pancreatitis, different therapeutic regimens including imipenem; third generation cephalosporins, piperacillin, fluoroquinolone and metronidazole are helpful.

Norfloxacin, colicicine and oral amphotericin can be used as intestinal antimicrobial agents for prevention.

The figures 1 and 2 show the detailed therapeutic approach in acute and recurrent pancreatitis (9, 15, 21, 25, 27, 41).

During the treatment, resuscitation of fluid, control of the involvement of other organs, prevention of shock and infection control should be considered. Then the diagnostic modalities should be performed to identify the possible underlying causes of pancreatitis. In recurrent cases, treatment should be followed by the algorithm for therapeutic approach. In idiopathic recurrent pancreatitis, the genetic test of cystic fibrosis transmembrane conductance regulator (CFTR) and identification of trypsinogen cationic gene

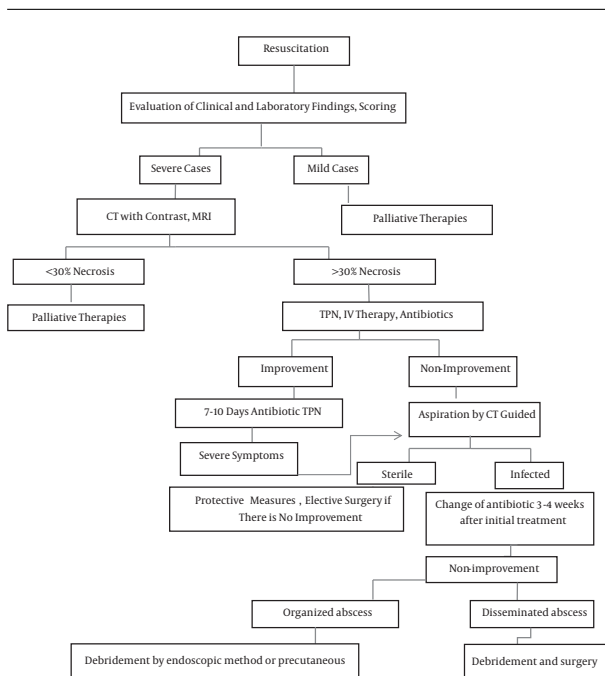


Figure 1. Treatment of Severe acute Pancreatitis

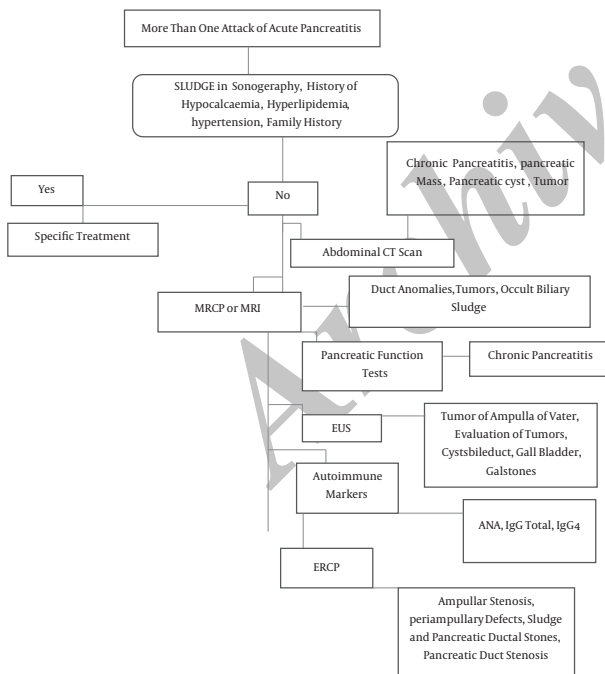


Figure 2. Algorithm Dealing With Acute or Recurrent Pancreatitis

with known causes (18, 42, 43).

4. Conclusions

In conclusion, the early diagnosis and the appropriate treatment can contribute to a better outcome for the children and adolescents with acute pancreatitis and to prevent the immediate and late complications related to the disease. More studies are required to better explain other aspects related to the diagnosis and treatment of acute pancreatitis in children.

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mutations are recommended. Laparoscopic cholecystectomy is recommended for cases of recurrent pancreatitis

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