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Acute Pancreatitis in Infants and Children

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Acute pancreatitis is being encountered more often in children due to antimetabolite therapy, accidental injury, and traumatic battering. Pancreatitis may occur in the absence of traditionally elevated serum amylase and lipase, and initial diagnosis may depend upon ultrasonography. Traditional therapy of enteric rest with nasogastric suction has been supported by the use of parenteral nutrition. Newer pharmaceutical agents have been ineffective in altering the course of the illness or in preventing complications of pseudocyst or abscess.

PANCREATITIS

Acute pancreatitis is one of the major abdominal catastrophes of all age groups [1-27]. Once considered unusual in children, the disease is being seen with increasing frequency, and most pediatric centers now treat five to ten acute cases per year. The increase in the incidence of the disease from a previously reported figure of 1 in 500,000 children is due not only to better recognition, but also to a rise in the number of infants and children subjected to blunt abdominal trauma and to the use of therapeutic agents which may cause pancreatitis.

Etiology

In approximately one-third of patients no cause for the disease is identified. However, trauma is now responsible for 30 to 40 percent of the cases of acute pancreatitis seen in children, a significant rise from figures of 13 and 15 percent reported five to 15 years ago. Abdominal trauma is most often caused by bicycle or sledding injuries, but is now being recognized in infants subjected to parental battering [8,9].

The pancreas lies fixed in the epigastric region behind the stomach and duodenum and anterior to the vertebrae. Its consistency is soft and its vascular supply lush, all rendering it susceptible to injury by a sharp or blunt blow projected to the upper abdomen. The poorly developed abdominal wall musculature and small anterior-posterior diameter of the abdomen in children increases the risk of pancreatic injury over that in the adult. Such trauma may cause contusion, laceration, or complete transection of the pancreas.

At the Yale-New Haven Hospital, drug-related pancreatitis is the second most common cause of the illness (30 percent) in children. L-asparginase, used primarily for the treatment of leukemia, has caused the most fulminant disease. The onset may occur days to weeks after initiation of therapy or up to several weeks after its termination [13]. Valproic acid, used increasingly for the treatment of seizures,

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causes not only hepatitis, but pancreatitis. Similarly, chlorthiazide and related thiazides have caused pancreatitis. Steroids are often implicated in the etiology of pancreatitis, and, in a review by Jordan and Ament [5], they were responsible for 20 percent of their cases. Steroid-induced pancreatitis occurs twice as often in boys as in girls and usually follows a change in dosage in either an upward or downward direction [12]. Focal pancreatic lesions may be found in patients taking steroids who have no clinical signs of pancreatitis. Pathologic lesions in patients with steroid-induced pancreatitis have been epitheloid proliferation of the ducts, inspissated secretions, and dilated atrophic acinai. Ethanol abuse, the most common cause of pancreatitis in the adult, is an unusual factor in the child, but has been reported to have caused pancreatitis in one 12-year-old Brazilian boy [14]. With the early use of alcohol in adolescents, it will undoubtedly be recognized more often as a causative agent. Other drugs causing pancreatitis are listed in Table 1. The mechanism of drug-induced pancreatitis remains unknown, although speculation exists as to the possibility of the drug binding to macromolecules on the pancreatic cell membranes, resulting in cell death.

Anatomic malformations contribute to the cause of pancreatitis in 10 to 15 percent of the patients by causing obstruction to pancreatic flow [27]. The most common anatomic lesion is stenosis or hypertrophy of the sphincter of Oddi. Other causes are impaction of the pancreatic duct by gall stones or obstruction of the duct by an annular pancreas or choledochal cyst. Four percent of individuals with pancreas divisum (non-fusion of the dorsal and ventral ducts) develop pancreatitis, which is due in the majority to stenosis at the orifice of the dorsal duct [24,25]. Treatment by sphincteroplasty is successful in fewer than 60 percent, suggesting that this anomaly in many patients may be only coincidental. An extremely rare cause of pancreatitis is an intrapancreatic duplication cyst of duodenal or gastric origin. An infectious origin is presumed likely in infants with pancreatitis because gram-negative organisms have been isolated from nearly two-thirds of affected patients [11]. Mild pancreatitis is not unusual in patients with systemic viral infections and may be found in up to 15 percent of those with mumps. Epigastric pain and vomiting occur four to five days after the onset of the parotid swelling or may rarely be only clinical manifestations of mumps infection [18]. It is of interest that diabetes mellitus has been reported in children who have had earlier evidence of mumps, coxsackie, or rubella infection [21]. Pancreatitis has also been associated with infection by adenovirus, reovirus, echovirus, and mycoplasma virus pneumoniae [17–19]. Interstitial pancreatitis has been reported in an infant who died from congenital rubella syndrome. Reye's syndrome, when accompanied by clinical and laboratory findings of pancreatitis, carries an extremely poor prognosis, for the pancreatitis is usually hemorrhagic in type [20].

The metabolic causes are multiple [1,4,11]. Hyperlipoproteinemia of types I, IV, and V may be associated in up to 8 percent with acute pancreatitis. Usually the lipid levels are well above 1,000 mg/ml, but during the acute attack the serum amylase may be normal. Cystic fibrosis, an inherited disorder which is usually characterized by pancreatic insufficiency as well as respiratory symptoms, may at times present with or have concomitant acute pancreatitis [15]. This inflammatory lesion often develops in adolescents and in those with a milder form of the disease. Hyperparathyroidism, although rare, may cause pancreatitis in children and often is associated with an intraductal calculus.

Vascular diseases such as the hemolytic-uremic syndrome and systemic lupus

TABLE 1
Causes of Pancreatitis

A. Traumatic	
B. Drug-induced	Corticosteroids
	Chemotherapeutic agents (i.e., L-asparginase)
	Valproic acid
	Chlorthiazides
	Azulfidine
	Alcohol
	Ethacrinic acid
	Furosemide
	Azothioprine
	Oral contraceptives
	Tetracycline
	Cimetidine
	Dilantin hypersensitivity
C. Infection	Mumps
	Measles
	Post varicella
	Rubella
	Hepatitis A and B
	Influenza A
	Coxsackie B
	Mycoplasma pneumoniae
	Leptospirosis
	Ascaris
	Hydatid cyst
	Reye's syndrome
D. Metabolic	Hyperlipoproteinemia type I, IV, and V
	Cystic fibrosis
	Hyperparathyroidism
	Refeeding after fasting
	Uremia
	Vitamin A or D deficiency
	Glycogen storage disease type I
	Scorpion bites
E. Anatomic defect	Pancreas divisum (?)
	Choledochal cyst
	Anomalous insertion of bile duct
	Duodenal duplication cyst
	Ductal stenosis of sphincter of Oddi
	Annular pancreas
	Cholelithiasis
	Posterior perforation of peptic ulcer
F. Hereditary	
G. Vascular disease	Vasculitis
	Hemolytic-uremic syndrome
	Systemic lupus erythematosus
H. Idiopathic	

erythematosus may demonstrate pancreatitis as part of their clinical spectrum [26]. Accidental hypothermia has caused intravascular coagulation and pancreatitis [22].

Refeeding pancreatitis is no longer a rare entity and has been noted in athletes, particularly wrestlers who diet to attain a low weight and who eat heavily after a match. Recently it has been reported in anorectics who are force-fed a high caloric diet [16]. Speculation exists as to whether these patients may have a relatively mild ductal stenosis or obstruction which has been accentuated by a sudden outpouring of enzymes.

Hereditary pancreatitis occurs in an autosomal dominant pattern with attacks or recurrent abdominal pain having their onset between infancy and adolescence [11,23]. In a number of patients, stenosis of the sphincter of Oddi has been identified at surgery or at radiologic examination. After repeated attacks of acute pancreatitis, there is eventual calcification in the pancreas. An inconstant amino acid urea with lysine and cystine is found in those from American families and taurine in those from English ones. Other amino acid ureas consist of lysine, cystine, and arginine or histidine. One kindred had hemorrhagic phenomena and increased sweat electrolytes without other signs compatible with cystic fibrosis.

Pathogenesis and Pathophysiology

The pathophysiology of pancreatitis includes three critical ingredients: *(1)* disruption of acinar or ductal integrity, *(2)* leakage of pancreatic enzymatic secretions into tissue spaces, and *(3)* activation of proteolytic and lipolytic enzymes. Although gross descriptions of the pancreas at laparotomy describe edematous, necrotizing, or hemorrhagic pancreatitis, autopsy examinations present terminology such as hemorrhagic, necrotizing, suppurative, edematous, or interstitial pancreatitis [6]. It is best to consider pancreatitis in terms of interstitial, hemorrhagic, or necrotizing. Interstitial pancreatitis, the milder form associated with fewer complications, is characterized by inflammation, edema, proliferation of fibroblasts, and collagen deposition within acinai. There is little necrosis and only isolated areas of fat necrosis. The disease is mild, usually associated with viral infections and persists for two to three days' duration. Hemorrhagic pancreatitis, on the other hand, is severe and the entire pancreas or large areas of it become necrotic and hemorrhagic with destruction of normal architecture. Jaundice and hyperbilirubinemia are secondary to spasm of the sphincter of Oddi. Ascites and pleural effusion may develop during the acute attack.

The direct release of enzymes from pancreatic damage causes autodigestion of the organ itself [28–32]. Those enzymes entering the peritoneal cavity digest protein and fat components to contribute to peritonitis. Hematologic and lymphatic spread of these same components is responsible for the systemic complications of pancreatitis [28,29]. Fat necrosis secondary to circulating pancreatic lipase has been described and causes tender erythematous subcutaneous nodules, polyarthritis, fever, eosinophilia, soft tissue swelling, and bone pain. Bone lesions associated with intramedullary fat necrosis may be seen on skeletal roentgenograms and occur in 10.4 percent of cases [30]. There is medullary fat necrosis, cortical destruction, and new periosteal bone formation. The lesions are best seen in the short bones of the hands and feet. Fat embolism may also occur during acute pancreatitis and cause significant morbidity. The syndrome of pancreatic encephalopathy presenting with mental confusion, muscle spasm, seizure activity, restlessness, combativeness, stupor, or coma have been attributed to cerebral fat embolization [31].

Acute renal failure associated with pancreatitis may be secondary to refractory hypovolemia, or to fat emboli which cause ischemic, aseptic necrosis with tubular atrophy and interstitial fibrosis [32].

The primary cause of early death is refractory hypotension which progresses to irreversible shock and organ failure. This is due to massive losses of blood and plasma caused by autodigestion of blood vessel walls. The situation is further aggravated by action of vasoactive peptides activated by kallekrein which is released into the lymphatics and plasma. Abnormalities of the clotting system may occur during the acute phase of acute pancreatitis, and disseminated intravascular coagulation has been demonstrated in many patients dying of severe necrotizing pancreatitis. The local release of trypsin has been shown to activate the clotting sequences.

Patients with severe pancreatitis are often hypocalcemic, but tetany or other clinical manifestations are rarely present. Hypocalcemia is often attributed to binding of calcium in areas of fat necrosis, but recently data have suggested alterations in levels of serum calcitonin and/or glucagon as the primary cause. A low serum calcium in acute pancreatitis may be associated with a low serum albumin and therefore values, when corrected, are usually normal. In one recent series, hypocalcemia, seen in 67 percent of patients, dropped to 11 percent when appropriately corrected for serum albumin levels.

Respiratory insufficiency is a significant cause of morbidity, although it is often undetectable early in the course of disease [33]. It may increase rapidly in severity and lead to sudden death. The factors most commonly implicated in its pathogenesis are abdominal distention, pain and guarding, retroperitoneal edema, elevation of the diaphragm, and pleural effusions. Pleural effusions occur in up to 20 percent of all patients with acute pancreatitis. They are usually located in the left chest and are often hemorrhagic. Diffuse pulmonary disease occurs in the more severely ill patients and in the presence of true persistent hypocalcemia. This syndrome often manifests itself within one week after onset of pancreatitis and leads to rapidly increasing dyspnea, cyanosis, and hypoxemia. It has been reported to occur in approximately 1 percent of all affected patients and may be associated with a mortality near 50 percent. The etiology remains obscure, but fluid load, aspiration, hypotension, hypoalbuminemia, fat embolization, and a direct effect on the vasculature or its permeability have all been suggested as etiologic factors.

Symptoms

Although severe traumatic pancreatitis may present immediately after injury with the patient in shock and having a rigid abdomen, the symptoms are usually more insidious and the diagnosis may not be considered until clinical deterioration occurs. Often, traumatic pancreatitis may present weeks after an injury, with the individual having no recollection of direct trauma. Pain is the major presenting symptom and occurs in more than 90 percent of patients with acute pancreatitis. The pain is often excruciating and accompanied by nausea and vomiting. It may, however, vary in character, being mild or severe, constant or intermittent, unrelieved by vomiting. The children often lie quietly on their sides with their knees flexed. The physical findings do not always correlate with the severity of the underlying disease. Tachycardia is usually present and the abdomen is distended and tender to palpation. Bowel sounds, which are present early, may disappear with the development of ileus. There is usually some guarding in the epigastrium and the patient may describe pain radiating into the back. A rigid abdomen is rare unless the pancreatitis is accom-

panied by a visceral perforation or severe intrapancreatic hemorrhage. The cutaneous signs of acute pancreatitis are seen infrequently: these include early morbilliform rashes secondary to subcutaneous fat necrosis, livido reticularis, Turner's sign (a bluish discoloration of the flanks due to fat necrosis or seepage of blood-stained fluid into the subcutaneous tissue), and Cullen's sign (a similar bluish discoloration in the periumbilical area).

Diagnosis

Immediate diagnostic tests are an elevated serum amylase and lipase. The serum amylase is normally less than 150 μg/dl and lipase less than 1.5 units/ml. The serum amylase is elevated in 95 percent of patients with acute pancreatitis but may be elevated in other conditions: i.e., macroamylasemia, intestinal obstruction, ovarian pathology, mumps, parotid or salivary gland lesions, renal insufficiency, hepatitis, perforations of the small bowel, or acute appendicitis [34–36]. The serum amylase rises within several hours after the onset of symptoms and returns to normal in several days. The urinary amylase level (normal, 300 units/hour) remains elevated for at least one week after an attack and can be used to document disease after serum values have fallen. Urinary amylase/creatinine clearance may be helpful in distinguishing the patient with pancreatitis, as a ratio greater than 6.5 percent is suggestive of acute pancreatitis. False negatives can occur in renal failure and false positives have been reported in diabetic ketoacidosis, in fulminant alcoholic liver disease, and in burn patients. This test is not infallible and its value is now controversial. The serum lipase rises approximately 24 hours after symptoms are present and remains elevated for about ten days. Elevations above 1.5 units correlate with true pancreatitis. The degree of elevation of either enzyme does not correlate with the severity of the disease or its prognosis.

Anemia may denote a severe hemorrhagic pancreatitis and is not present in mild disease. A fall in hematocrit of greater than 10 points during the initial 48 hours is correlated with a poor prognosis [37,38]. Hemoconcentration may occur secondary to fluid loss. Leukocytosis between 10,000 and 30,000 wbc/cm^3 with a shift to immature polymorphonuclear leukocytes is commonly seen. A leukocyte count greater than 16,000 wbc/cm^3 may be associated with increased morbidity. Prolonged leukocytosis and fever indicate abscess or another infectious complication [39]. The erythrocyte sedimentation rate is elevated in half of the patients.

Hyperglycemia may be present in the acute stage, although some patients are hypoglycemic. Hypercalcemia, as noted earlier, is frequent. Hyperlipemia is due to several factors: decreased plasma lipoprotein lipase activity, increase in serum glycerides, and absorption of fat from intraperitoneal fat necrosis. Abdominal films of the abdomen may show *(1)* localized ileus with "sentinel loop," a loop of dilated jejunum in the mid-epigastrium or left upper quadrant adjacent to the pancreas; *(2)* "colon cut-off sign" representing distention of the transverse colon with collapse of the descending colon in areas adjacent to the pancreatic inflammation; *(3)* duodenal distention with occasional air fluid levels or duodenal edema. Other findings are loss of the psoas shadow, distortion or greater curvature of the stomach, colonic dilatation, or increased epigastric soft tissue density. Calcification of the pancreas is evidence of earlier attacks of acute pancreatitis. Ultrasonography of the pancreas has been the procedure of choice as a non-invasive, diagnostic aid in the assessment of acute pancreatitis [40–43]. It has proven to be the single most valuable clinical tool in following the pancreatic size in determining whether or not abscess or

pseudocyst is developing. Initially, the normal cobble-stoned appearance becomes more sonolucent as the pancreas becomes edematous. Abscess and pseudocyst are easily differentiated by their characteristic echo-free appearance. Phlegmons may appear as areas of pancreatic enlargement with numerous internal echoes reflecting the solid consistency. The role of modern-day ultrasonography in monitoring the size of a pseudocyst and in determining the optimal time for surgery cannot be overemphasized. Nuclear imaging of the pancreas using Se75 is complicated by the adjacent liver, which readily incorporates the isotope and has largely been replaced by ultrasonography or computerized tomography. The latter procedure is associated with considerable radiation exposure and, although preferable for the detection of smaller pancreatic lesions, offers no greater advantage over ultrasonography in the management of patients with pancreatitis. Retrograde pancreatic studies are contraindicated in the presence of acute disease.

Therapy

The therapy of acute pancreatitis is based upon an understanding of the pathophysiology involved (Table 2) [39]. Primary goals are *(1)* maintenance of adequate circulating intravascular volume, *(2)* minimization of pancreatic exocrine activity, and *(3)* prevention or treatment of complications associated with acute pancreatitis [6,11,44–50]. Initially, the patient is fasted and nasogastric suction applied to reduce vomiting and distention and to decrease secretin release secondary to duodenal acidification. Intravenous fluids and/or colloid are administered to maintain an adequate intravascular volume. The hemoglobin, hematocrit, white blood count, serum calcium, glucose, and electrolytes are monitored closely, and therapy adjusted as indicated. Merperidine or pentazocin are recommended for relief of pain rather than opiates. There is little evidence to suggest that cimetidine reduces pancreatic secretion by inhibiting gastric acid production [45,46]. Anticholinergic drugs such as atropine have been suggested, but controlled studies have failed to show their effectiveness. Glucagon, a hormone produced by the pancreas, has been shown to suppress pancreatic function when given in sufficient doses, but recent controlled trials have failed to document any true benefit. The use of prophylactic antibiotics has been shown not to prevent abscess formation or septic complications [47,48]. Such use may predispose the patient to develop infection by organisms which are resistant to common antibiotics. In recent years, effort has been directed toward inhibiting the actual process of pancreatitis. The most successful of these efforts in animal models has been with the drug aprotonin. Unfortunately, the drug is effec-

TABLE 2
Therapy for Acute Pancreatitis

1. Fast the patient
2. Maintain adequate intravascular volume
3. Nasogastric suction
4. Analgesia (avoid opiates)
5. Follow metabolic parameters closely:
   a. Glucose
   b. Calcium
   c. Electrolytes
   d. Hemoglobin
6. Intravenous alimentation if nutritionally indicated

tive only if administered prophylactically and seems to have no effect once the proteolytic sequence has begun.

Improvements in elemental nutrition and hyperalimentation have markedly improved the prognosis for a patient with prolonged acute pancreatitis. Oral feeding should not be reinstituted in the patient until all abdominal tenderness, fever, and leukocytosis have vanished; ileus has resolved; and serum amylase and lipase levels have returned to normal. Initial feeding should contain carbohydrate and little, if any, fat or protein, which stimulate pancreatic secretions. Parenteral lipids should be withheld until the acute illness has subsided [44].

Pleural effusions may respond to therapeutic taps, and diffuse pulmonary injury is managed as in any other patient with the respiratory distress syndrome. Aggressive fluid or colloid therapy is usually effective in correcting hypotension, but occasionally patients may require pressor agents. Hypoxemia is more frequent than believed and occurs even in those with mild disease. Renal, hematologic, central nervous system, or cardiovascular complications require aggressive and supportive therapy. Since most of the severe systemic complications are presumed to be secondary to enzyme and vasoactive toxins that have been released from the peritoneal cavity, it has been postulated that removal of these substances may reduce the morbidity and mortality of acute pancreatitis [49,50]. Experimental and controlled clinical trials of non-operative peritoneal lavage have had some limited success [6]. Experience with this procedure in children is small and at present it cannot be recommended as a routine measure. Pancreatitis as the result of trauma may involve actual anatomic fractures of the gland, parenchyma, and/or duct transection. In such cases simple debridement and drainage are inadequate and subtotal pancreatectomy and distal drainage are required. Pancreatitis resulting from ampullary obstruction by a duodenal hematoma will often not resolve until the hematoma is evacuated. Factors associated with poor prognosis are itemized in Table 3.

Complications

An acute episode of pancreatitis which persists into the second or third week often becomes complicated by the formation of an inflammatory mass in 15 percent of patients. With this there are increased abdominal tenderness, elevation of temperature, and leukocytosis. The mass may represent a phlegmon, abscess, or pseudocyst [6,11]. Phlegmons themselves may develop into a well-defined pseudocyst or become secondarily infected to form an abscess. Abscess develops in approximately

TABLE 3
Laboratory Parameters Indicating Poor Prognosis

Admission:
White blood count > 16,000/mm^3
Blood glucose > 200 mg/dl
Serum lactic dehydrogenase > 350 IU/L
Serum glutamic oxaloacetic transaminase > 250 u
During first 48 hours:
Hematocrit fall > 10 points
Blood urea nitrogen rise > 5 mg/dl
Serum calcium < 8 mg/dl
Arterial PO_2 < 60 mm Hg
Base deficit > 4 mEq/L

5 percent of all patients with acute pancreatitis and carries an associated mortality of 22 to 57 percent. Abscess formation results from secondary infection or necrotic devitalized tissue and the bacteria recovered in over 90 percent of abscesses are enteric flora. Antibiotic therapy with external surgical drainage is mandatory. A pseudocyst consists of collections of blood, pancreatic enzymes, tissue fluid, and debris from the pancreas and develops within several weeks after the onset of acute disease [51]. Early, it contains no mature fibrous capsule and may be reabsorbed (less than 10 percent). The mortality of sudden rupture of a pseudocyst is so high that medical management should only be attempted when very close observation can be performed over a period of weeks. Surgical intervention should be attempted only after the cyst is mature (between six to eight weeks) with the cyst marsupialized and drained internally to the stomach or duodenum. Uncommonly, major arterial hemorrhage has been reported secondary to pseudocyst erosion into major arteries supplying the intestine. Diabetes mellitus has been reported as a late complication of acute pancreatitis in children who have had prior viral infection. Pancreatic exocrine insufficiency is uncommon, since this requires destruction of 85 to 90 percent of the gland.

CONCLUSIONS

The incidence of acute pancreatitis in children is increasing primarily due to a rise in abdominal trauma and an increase in usage of drugs which are toxic to the pancreas. Despite the varied etiologies of pancreatitis, therapy is directed toward decreasing pancreatic exocrine function and support of the hemodynamic consequences secondary to release of pancreatic enzymes and toxins into the system. Although the course cannot always be correlated with the severity of disease in onset, a number of laboratory findings suggesting a poor prognosis have been identified. Despite numerous clinical trials with the use of agents considered to be effective in decreasing the severity of pancreatitis, none has demonstrated any significant therapeutic benefit. Intensive medical management of the patient with the use of intravenous or parenteral alimentation and careful scrutiny for the development of surgical complications remains the primary therapy.

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