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What Have We Learned About Acute Pancreatitis in Children?

Harrison X. Bai^{*}, Mark E. Lowe[†], and Sohail Z. Husain^{*}

^{*}Department of Pediatrics, Yale University School of Medicine, New Haven, CT

[†]Department of Pediatrics, Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center, Pittsburgh, PA

Abstract

Pediatric pancreatitis has received much attention during the past few years. Numerous reports have identified an increasing trend in the diagnosis of acute pancreatitis in children and key differences in disease presentation and management between infants and older children. The present review provides a brief, evidence-based focus on the latest progress in the clinical field. It also poses important questions for emerging multicenter registries to answer about the natural history and management of affected children with pancreatitis.

Keywords

acute pancreatitis; children; infants; pediatric; toddlers

Pancreatitis is defined as the histological presence of inflammation within the parenchyma of the pancreas. Acute pancreatitis is a reversible process characterized by the presence of interstitial edema, infiltration by acute inflammatory cells, and varying degrees of necrosis, apoptosis, and hemorrhage (1). By contrast, chronic pancreatitis causes irreversible changes in the anatomy and function of the pancreas. Fibrosis and infiltration of chronic inflammatory cells can lead to exocrine or endocrine failure or both (2). In the present review, we focus on acute pancreatitis in children. After a brief discussion of pathophysiology, we provide, using the limited pediatric studies on this subject, estimates on disease burden and incidence. Then we discuss how children present with acute pancreatitis and how they are managed. We end with suggested areas for further research.

PATHOPHYSIOLOGY

The pathophysiology of acute pancreatitis remains obscure (Fig. 1). The current belief is that despite having multiple etiologies, inflammation in acute pancreatitis appears to be the result of a common pathway. Aberrant nonphysiological calcium signals within the pancreatic acinar cells are generated first, followed by the premature activation of intraacinar pancreatic proenzymes, or zymogens, within the acinar cells (3). Activated zymogens, in particular the protease trypsin, are thought to mediate pancreatic acinar cell injury and, to an extent, the production of cytokines such as tumor necrosis factor- α (4). These cytokines lead to an acute inflammatory response and varying degrees of extrapancreatic inflammation. Pancreatic ischemia can occur secondary to the ensuing inflammation, or in some cases may

cause pancreatitis (5). There are several protective mechanisms within the pancreas to limit the development of pancreatitis. These include compartmentalization of pancreatic enzymes and endogenous trypsin inhibitors such as SPINK1 and autodegradation of trypsin (Fig. 1).

An area of great interest is the mechanisms that allow the pancreas to recover and regenerate after pancreatitis. Rosiglitazone and melatonin have been reported to promote pancreatic regeneration after arginine-induced acute pancreatitis (6,7). In rosiglitazone- or melatonin-treated rats, lower levels of pancreatic enzymes, higher rates of DNA synthesis, and lower histopathological scores were found when compared with controls (6,7). It is hoped that these investigations and others will elucidate the mechanisms leading to pancreatitis and, more important, help to devise novel therapies that target the disease.

BURDEN OF DISEASE IN CHILDREN AND RISING TRENDS

Acute pancreatitis in children is a costly and increasingly recognized disease. As in adults, the incidence of acute pancreatitis in children also appears to be on the rise. Several studies have documented an increase during the past 10 to 15 years. Lopez (8) first reported an increase in admissions for acute pancreatitis at the Children's Hospital of Dallas from 5 to 113 patients between 1993 and 1998. This was followed by Werlin et al (9), who showed a 64% increase from 1996 to 2000. Similar studies from Mexico, Australia, New Haven, and Pittsburgh have corroborated this trend (10–13).

The reasons for the increase are not entirely clear and may be multifactorial. The study from Australia suggested that there were an increasing number of patients who presented with systemic illness and developed pancreatitis as a complication of their systemic illness (13). Park et al (11) showed that about half of the rise in cases could be attributed to an increasing trend among families and pediatricians to send children to tertiary care centers instead of community hospitals. Thus, a greater number of children are being seen at these institutions, where studies of trends are performed. Most recently, the group from Pittsburgh suggested a strong correlation between the number of amylase and lipase tests and the rising incidence of disease, suggesting that there is now a greater proclivity to consider a diagnosis of acute pancreatitis in children (10). In summary, the increase in incidence may be related to multiple factors including changing trends in pancreatitis etiologies and in referral and diagnosis.

Rough estimates about disease burden can be calculated by extrapolating from regional studies. Because acute pancreatitis is not a chronic disorder, the burden of disease is best appreciated using incidence estimates. Two studies have examined the incidence of acute pancreatitis in children, one from the United States (the Children's Hospital of Pittsburgh), in which estimates of incidence are 13.2 cases in 100,000 children per year, or about 1 in 7500/year (10), and the other from Australia (the Royal Children's Hospital, Melbourne), which estimates an incidence of 3.6 cases in 100,000/year, or about 1 in 28,000/year (13). The incidence estimate for the United States, for example, suggests that there are about 11,000 American children who present with acute pancreatitis each year. Factoring in average hospital stays for children with acute pancreatitis and daily hospital costs, the inpatient cost alone is about \$200 million/year. The added cost of prolonged hospitalization due to complications of the disease, intensive care unit stay, surgical or interventional procedures, and imaging and biochemical testing is inestimable because data are lacking. There is also lost work time for family members and the outpatient costs of follow-up visits and procedures. These estimates demonstrate that acute pancreatitis is a significant health and economic burden to society, and is much more common than previously thought.

DIAGNOSING ACUTE PANCREATITIS

Because histological sampling of the pancreas is impractical in the overwhelming majority of patients, pancreatitis is diagnosed by clinical presentation, serum biochemical profiling, and imaging modalities. Gastroenterologists caring for adults have adapted diagnostic criteria that were derived from a consensus conference held in Atlanta in 1992. These Atlanta criteria require that patients meet at least 2 of the following 3 parameters to qualify as having acute pancreatitis: typical abdominal pain, elevated amylase/lipase >3 times the upper limit of normal, and/or confirmatory findings on cross-sectional abdominal imaging (1).

Historically, pediatricians have applied criteria for the diagnosis of pancreatitis in adults to children. Adults generally present with nausea, vomiting, and abdominal pain. Classically, pain is localized to the epigastrium but can become diffuse and even develop into rebound tenderness. Other features include fever, ileus, and jaundice. The most commonly used biochemical criterion for acute pancreatitis is a 3-fold elevation in the serum of the pancreatic secretory enzymes amylase and lipase. By radiography, cross-sectional imaging by computed tomography (CT) scan or magnetic resonance imaging or ultrasound of the pancreas may reveal edema with fluid collection, peripancreatic fat stranding, or necrosis. Recently, pediatricians have come to realize that the adult teaching may not apply to children. Variation in age, developmental stages, and environmental exposures in children may influence the presentation of children with acute pancreatitis.

HOW DO CHILDREN WITH ACUTE PANCREATITIS PRESENT?

There have been more than 28 studies characterizing children with acute pancreatitis since 1965 (Table 1). All of them are retrospective. Most are from the United States, but many others come from other regions of the world. Most studies had only 1 dozen to 50 patients, but 4 studies in particular, from Pittsburgh, New Haven, Wisconsin, and Australia, comprised 87 to 280 patients each (14). These studies differ in several key areas: the proportion of children belonging to various pediatric age groups, severity of disease, diagnostic inclusion criteria, and etiologic classification. Notwithstanding these limitations, several important trends relating to presentation, management, and outcome emerge. Below we highlight these common themes in children with acute pancreatitis from the literature.

Clinical Presentation

In pediatric studies of acute pancreatitis, 80% to 95% of patients presented with abdominal pain (15–20). A notable exception is a large study conducted in Wisconsin that reported that only two thirds of patients had abdominal pain (9). The most common location of pain was in the epigastric region (62%–89% of cases) (15,21,22). However, epigastric pain was associated with back pain <10% of the time (9,17), and radiation to the back in only a minority of cases (1.6%–5.6%) (19,20,22). Diffuse abdominal pain was reported in 12% to 20% of patients (15,19,20). Guarding was noted in 2 studies (29% and 37%, respectively) (15,17). In nonverbal children, irritability was a common presenting complaint and may be a surrogate for complaints of pain in this age group (14) (Table 2).

The second most common symptom was nausea or vomiting, which was reported in 40% to 80% of patients (9,12,16,18–24). A study from Toronto reported bilious vomiting in 20% of patients, with none of these children having mechanical bowel obstruction (18). Similarly, ileus was reported in a study from Mexico in just under half of the patients (12). Abdominal distension was seen in 21% to 46% of patients (15,16,18,19). Other symptoms included fever, jaundice, ascites, and pleural effusion. In a study from Taiwan, a palpable abdominal mass was noted in one quarter of the cases (22). The most common mass was an abdominal

pseudocyst (80% of masses) (22). The finding has not, however, been reported in other studies to the same extent. In all of these studies, only 1 patient from Toronto had a positive Grey Turner sign, defined as the presence of ecchymoses of the flank (18).

When infants and toddlers were compared with children between 3 and 20 years of age, fewer presented with abdominal pain (43% vs 93%), epigastric tenderness (57% vs 90%), and nausea (29% vs 76%) (21). In a study of 87 infants and toddlers from Pittsburgh, 16% presented with abdominal distension and 40% presented with fever, an uncommon presentation in older children (14).

Biochemical Presentation

Elevations in serum amylase and lipase are the most common biochemical determinants of pancreatitis. In pediatric studies, the sensitivity of the amylase test in diagnosing pancreatitis has ranged from 50% to 85% (9,12,16,17,21,22,24,25). Lipase was only marginally more sensitive than amylase in most studies (9,12,16,21,22). Although Park et al (21) noted a sensitivity of 77.3% for lipase, which was about 25% more sensitive than amylase in their study, the sensitivity for amylase or lipase ($>3\times$ upper limit of normal) combined was only 4% higher than lipase alone. In addition, peak lipase levels were about 5-fold higher than amylase levels in children with acute pancreatitis. However, this does not mean that the amylase test is dispensable because Werlin et al (9) reported 4 patients with elevated amylase alone. In addition, the authors' unpublished experience at St Louis Children's Hospital suggested that about 10% of patients with acute pancreatitis had only elevated amylase, including 2 patients with clear radiographic evidence of acute pancreatitis.

In infants and toddlers, studies from Pittsburgh and New Haven reported that lipase was elevated in 100% of patients, but amylase was elevated in only about 40% to 60% (14,21). This discrepancy may be attributed to developmental differences in the expression of the pancreatic enzymes during the first few months of life (26). Both amylase and lipase expression levels increase after birth with amylase often showing a slower rate of rise. Notably, both enzymes may be elevated in other illnesses as well, although it must be remembered that it is impossible to eliminate the possibility of pancreatitis with certainty (Table 3). In particular, serum amylase elevations can arise from nonpancreatic sources such as the salivary gland and intestine or result from reduced renal clearance.

Additional biochemical parameters to diagnose acute pancreatitis include the serum cationic trypsinogen, which was shown by Weizman and Durie (18) to have greater sensitivity than amylase. Newer tests such as serum or urine measurement of trypsinogen activation peptide have not been examined in children (27,28).

Radiographic Presentation

Imaging modalities have increasingly played a role in the diagnosis of acute pancreatitis. Ultrasound is particularly appealing as an initial imaging tool because it does not subject children to ionizing radiation and it is widely available. In addition to providing complementary information on a diagnosis of pancreatitis, it can be used to evaluate for multiple other causes of an acute abdomen (eg, appendicitis, intussusception, volvulus). Furthermore, ultrasound is superior to CT scan in detecting gallstones as a cause of pancreatitis (29). The 2 main disadvantages of ultrasound are that it is operator dependent and overlying bowel gas or an obese abdomen can obscure the pancreas. Diagnostic features at presentation using abdominal ultrasound include pancreatic parenchymal changes such as pancreatic heterogeneity, edema, and peripancreatic fluid collections. The majority of children in recent studies had an ultrasound performed on presentation (56%–84%)

(9,12,14–19,21,22). In most studies, only about one third to half of the patients had ultrasonographic evidence of pancreatitis (9,12,18,21).

CT is generally not recommended to evaluate for pancreatitis on initial presentation, unless the diagnosis is unclear (30,31). However, it is useful several days into the diagnosis when pancreatic necrosis is suspected clinically (30–32). CT scan was performed in only about one third of children with suspected pancreatitis, but its sensitivity for parenchymal changes or peripancreatic fluid was only 60% to 75% (9,14,21,23). There are no current guidelines suggesting the use of MRI to diagnose pancreatitis. However, as this modality becomes more accessible and less time-consuming, it may have a role in the future (33).

With regard to infants and toddlers, the study from New Haven demonstrated that they were more likely to undergo ultrasound than older children (100% vs 78%; $P<0.05$) (21). The result is not surprising because imaging modalities to evaluate for pancreatitis are particularly useful in an age group in whom the diagnosis can be more elusive.

ETIOLOGIES OF ACUTE PANCREATITIS IN CHILDREN

Although in adults, the overwhelming majority of pancreatitis episodes are associated with gallstones or alcohol, in children the etiologies are much more diverse (Table 4). A clear cataloging of etiologies in childhood is complicated because a wide range of prevalence in etiologies has been reported in various studies. The variation in etiologies likely reflects the retrospective nature of the studies, which can be complicated by the bias or experience of the clinicians caring for the patients and incomplete investigations for etiologies. Also, the growing incidence and recognition of new etiologies result in the splitting of some categories listed in earlier reports. Examination of available data suggests that the top 5 etiologies of acute pancreatitis in children are biliary, medications, idiopathic, systemic disease, and trauma, followed by infectious, metabolic, and hereditary (8,9,11–14,18,22–24,34–37). Not surprisingly, alcohol is rarely reported as a cause of pancreatitis in children. In infants and toddlers, the etiologies resemble those reported for other pediatric age groups (14,21).

Biliary Disease

Biliary tract disease, referring to the presence of gallstones or sludge in the gallbladder, was seen in 10% to 30% of patients (9,11,12,14,16,18,22,23,34–36). In the study from New Haven, biliary causes also included structural defects such as pancreas divisum and anomalies such as sphincter of Oddi dysfunction; they made up 2.9% and 1.4% of the total number of patients with pancreatitis, respectively (11). Whereas in adults, biliary obstruction causing pancreatitis is almost exclusively due to stones or tumors, in children about 30% of biliary causes are attributed to sludge (9,11,14,35). Whether this difference is due to a larger percentage of children with biliary disease who had sludge/microlithiasis instead of full-fledged gallstones is unclear and requires further investigation. In most studies of children with biliary pancreatitis, children presented with abnormal liver function tests, particularly transaminase elevation and sometimes mild hyperbilirubinemia (12.5%) (35).

Most guidelines recommend removal of the stone by endoscopic retrograde cholangiopancreatography if the obstruction persists for 2 to 3 days or if cholangitis or worsening pancreatitis develops (30,31,38).

Whether to treat sludge is not clear, although there are some reports in children in which clinicians used the cholorectic ursodexoycholic acid to treat patients with sludge (39). However, it is unclear whether the improvement in pancreatitis and resolution of biliary obstruction from sludge were spontaneous or due to the medication.

In patients with cholelithiasis, cholecystectomy is recommended within 2 weeks by UK guidelines published in 2005 (38), but not beyond 4 weeks in an American Gastroenterological Association technical review from 2007 (40). However, there is no clear indication for cholecystectomy in sludge-induced biliary pancreatitis, unless the pancreatitis is recurrent (41).

Medications

Pancreatitis was attributed to medications in less than one quarter of children in most studies (8,9,11,12,18,22,34,36,37). The most common medications were valproic acid, L-asparaginase, prednisone, and 6-mercaptopurine (9,11,13,14,22,35). No clear mechanism has been delineated for the development of medication-induced pancreatitis. Interpretation of the cause-and-effect relation between drugs and pancreatitis is difficult and must be approached cautiously. For instance, many patients on prednisone have systemic illnesses that, in and of themselves, may predispose to pancreatitis.

Idiopathic

Patients with idiopathic pancreatitis ranged from 13% to 34% (8,9,11,13,14,18,22–24,34–37). Surprisingly, despite better detection modalities and an increased awareness of pancreatitis etiologies during the past 2 decades, there was no reduction in the proportion of idiopathic patients from earlier studies of children compared with more recent ones.

Multisystem Disease

Systemic disease was reported in about one third of patients (9,12–14,18,23). The systemic diseases most commonly associated with pancreatitis were sepsis, shock with or without sepsis, hemolytic-uremic syndrome, and systemic lupus erythematosus (9,11,14,18,35). An Australian study suggested that the observed increase in incidence of pancreatitis over 10 years was due to a greater number of patients presenting with systemic disease-associated pancreatitis (13).

Trauma

Trauma was seen in 10% to 40% of studies (8,9,11–14,18, 22–24,34–37). The common causes of traumatic pancreatitis were motor vehicle crashes, sports injuries, accidental falls, and child abuse (11,13,22). In a study of infants and toddlers, there was a pancreatic contusion on exploratory laparotomy and distal pancreatic resection (14).

Infections

Infectious causes were seen in <10% in most studies (8,9,11–13,18,22,34–36). Most often infections were suggested based on fever, upper respiratory tract symptoms, or a viral prodrome. It is difficult to determine whether there is a causal relation between the symptoms of infection and pancreatitis or it is simply a temporal association of a common event. Notably, the mumps virus was reported to be the infectious agent in several studies (17,35,37). Other infectious etiologies associated with acute pancreatitis in children include hepatitis A virus (42–45), rotavirus (46–48), hepatitis E virus (42,49), varicella (50,51), mycoplasma pneumonia (52), moraxella catarrhalis (53), adenovirus (54), and coxsackie B4 (55).

Metabolic

Metabolic causes were seen in about 2% to 7% of patients (9,11–13,18,34,36). The most common was diabetic ketoacidosis, followed by hypertriglyceridemia and hypercalcemia (8,9,11,12,36). Overall, patients with metabolic disorders were more likely to have recurrence of pancreatitis (21). This may be a result of recurrent metabolic disturbances, but

the correlation has not been well documented (56). Treatment depends on the underlying condition. In the case of hypertriglyceridemia, options include acutely reducing triglyceride level by administering intravenous fluids, lipid-lowering agents, or apheresis (57,58). Most cases of hypercalcemia were due to hyperparathyroidism and treated with parathyroidectomy (59).

Hereditary

Hereditary causes were seen in about 5% to 8% of patients (9,11,13,14,18,36,37). Mutations were most commonly found in the cationic trypsinogen gene (*PRSSI*), the pancreatic secretory trypsin inhibitor gene (*SPINK1*), and the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) (9,13,14). A recent review (60) by Whitcomb provides details on the loss of protective mechanisms due to genetic defects. It remains to be determined to what extent genetic factors or predisposition is involved in the pathogenesis of idiopathic acute pancreatitis.

Short-term Course

The mean length of hospitalization for children with acute pancreatitis was about 25 days (9,12). However, this number includes patients who were admitted for long periods for multi-system disease often unrelated to pancreatitis. Therefore, the median number of days is a more representative figure and was about 5 to 8 days in most large studies (9,14,21). Interestingly, this is the same length of stay reported in adults who were admitted with mild, acute pancreatitis (61). Only 1 pediatric study consisting of 50 children from several centers in Italy reported longer median hospital stays for children with both mild and severe disease (13 and 20 days, respectively) (37). This discrepancy may be reconciled by several factors, including varying degrees of pressure from health care delivery systems to reduce hospital stay. Infants and toddlers spent a significantly greater number of days in the hospital than older children (median 19.5 vs 4 days) (21).

Nutrition has emerged as an important treatment modality in pancreatitis. Just 2 decades ago, it was generally believed that patients with acute pancreatitis should be made completely nothing per ore at admission to rest the pancreas and thus reduce stimulation of pancreatic secretions. However, based on several large randomized controlled trials (62–64) on severe acute pancreatitis in adults, it is now accepted that early enteral feeding reduces complications of acute pancreatitis.

Most published guidelines recommend jejunal feeding 1 to 2 days after developing severe pancreatitis, but there may be a role for slow, continuous nasogastric tube feedings (65). This is an area of active investigation (www.clinicaltrials.gov NCT00580749) (66–68). Total parenteral nutrition (TPN) is generally not recommended unless a patient proves intolerant to enteral feeding.

Despite the body of literature and guidelines advocating enteral feeding, recent reports on children with acute pancreatitis demonstrate that actual practice sorely lags behind those recommendations. In most studies, 70% of patients were made nothing per ore at admission, 20% received TPN, and only 3% underwent enteral feeding (9,12,16,21). Infants and toddlers are much more likely to receive TPN than older children (64% vs 17%) (21). Pediatric trials of enteral feeding have never been performed. This is an area of potential effect in reducing morbidity from pancreatitis, including indices such as length of stay or refeeding pain.

Several prospective randomized controlled clinical trials have also compared whether it makes a difference to start patients with mild acute pancreatitis on a clear liquid diet versus a soft or low-fat diet. Sathiaraj et al (69) reported a significantly decreased length of

hospitalization in those receiving a soft diet (ie, savory cake made by steaming a batter consisting of fermented black lentils and rice, a pea and vegetable stew or chowder based on a broth made with tamarind and pigeon pea, curds mixed with rice for lunch and dinner) when compared with those receiving a clear liquid diet ($P<0.001$). Moraes et al (70) reported a similar result, albeit only in patients without abdominal pain relapse. Jacobson et al (61) reported no difference in the length of hospitalization between the 2 groups, but the solid diet provided more energy to patients.

Adequate intravenous fluid resuscitation is also an important supportive measure in the management of acute pancreatitis (71). Early, aggressive fluid resuscitation is generally advocated, but the optimal rate, type, and volume of fluid are not known even in adults (59).

It is increasingly thought that specialty care of these patients may have an effect on their course of disease (21). Notably, two thirds of children from the New Haven study underwent gastrointestinal consultation (21). The gastrointestinal consultation rate was also much higher in infants and toddlers, likely because pediatricians are much less comfortable dealing with pancreatitis in this age group.

LONG-TERM COURSE AND COMPLICATIONS

Complications in acute pancreatitis can be divided into early and late onset. Early-onset complications primarily include multi-organ dysfunction or shock (72). Two major organs involved are the lung and kidney. Patients can develop acute respiratory distress syndrome, pneumonia, or pulmonary effusion (73). This finding is corroborated by acute lung injury in experimental animal models of acute pancreatitis (74). Renal failure is also observed (75). Late-onset complications are mainly pancreatic necrosis and pseudocyst formation (72). Necrosis can be infected or noninfected. A pancreatic pseudocyst is defined as a homogeneous collection of amylase-rich pancreatic fluid that lacks an epithelial lining (59). A second type of collection, loosely termed “walled off necrosis,” is characterized by the presence of necrotic debris within a fluid-filled cavity (59).

Small pseudocysts not causing any symptoms can be managed conservatively (76). However, intervention is warranted for persistently symptomatic pseudocysts or those with the evidence of complications (eg, infection, bleeding) (77). The size of the pseudocyst is a poor indication because even large pseudocysts may resolve spontaneously. In the past, surgical drainage was the only therapeutic option (78). Percutaneous drainage has been reported to have a higher mortality (16% vs 0%), a higher incidence of complications (64% vs 27%), and a longer hospital stay (45 ± 5 days vs 18 ± 2 days) than patients treated by surgery (79). In recent years, radiographic, endoscopic, and laparoscopic drainage have played an increasing role (80). In a recent study, Jazrawi et al (81) reported 10 cases of successful endoscopic ultrasound-guided pseudocyst drainage in children.

In addition to complications from a single episode of acute pancreatitis, patients can develop recurrent episodes. A prevailing hypothesis, termed the sentinel acute pancreatitis event, states that recurrent acute pancreatitis can transition into chronic pancreatitis (82). However, there are no data on recurrent pancreatitis transitioning into chronic pancreatitis in children, except possibly in the case of hereditary pancreatitis (82). About 15% to 35% of children with acute pancreatitis have recurrence (9,11,12,22–24,34,37). The average number of recurrences per patient in the 13-year retrospective study from New Haven was about 2.7 episodes per patient (11). Notably, fewer infants had documented recurrence (7%–10%) (14,21). Recurrent pancreatitis was primarily seen in patients who had biliary anomalies, metabolic disorders, particularly hypertriglyceridemia, and idiopathic and hereditary pancreatitis (18).

In children, only a small percentage of patients were reported to have severe complications, as opposed to adults. Fewer than 6% of children went on to develop multiorgan dysfunction or pancreatic necrosis (9,13,21,37). Pseudocysts were formed in 10% to 20% (12,15–17,23,25,37,83), most often associated with a traumatic etiology (16).

Mortality of acute pancreatitis in children ranged from 0% to 11% (9,11–14,22,23,37). The higher end of the range could be inflated because many patients died as a result of their underlying disease instead of pancreatitis. Reasons for a lower number of deaths in children than in adults may include the virtual absence of alcoholic pancreatitis, an etiology known to carry a much higher mortality. In addition, adults may have lost important protective mechanisms with age that children have retained. Discovering these potential protective mechanisms may help elucidate treatments for both adult and pediatric patients with pancreatitis.

AREAS FOR FURTHER RESEARCH

As evidenced from the present review, virtually all of our information on acute pancreatitis in children is based on retrospective studies, most of which have a small number of patients. Furthermore, our practice parameters are completely derived from adult guidelines. It is clear that children present differently and have a more varied set of etiologies. Thus, to optimally care for children with acute pancreatitis, the pediatric community needs to critically examine several key areas relating to this disease.

There is a need to validate in children the criteria used in adults to diagnose acute pancreatitis. Knowing that clinical features such as abdominal pain or epigastric tenderness are less likely to be elicited in children and that amylase and lipase levels are lower in infants and toddlers, there is a need to critically examine diagnostic criteria of acute pancreatitis in this age group in particular. There are also few data to determine what imaging modality is best to diagnose and evaluate children for acute pancreatitis. Although transabdominal ultrasound is used most often and is more convenient, should there be a more prominent role for magnetic resonance cholangiopancreatography? Is it necessary to enhance ductal secretion using secretin, to detect ductal anomalies? How does magnetic resonance cholangiopancreatography compare with contrast-enhanced CT in detecting necrosis or pancreatic fluid collections? What is the complication rate of endoscopic retrograde cholangiopancreatography for gallstone extraction in gallstone pancreatitis in children? In the long term, do children with pancreas divisum associated with pancreatitis actually benefit from minor sphincterotomy? What are the long-term sequelae?

How does one reliably determine etiology of acute pancreatitis? Should etiologies be mutually exclusive, as in most studies? Recent experimental data suggest that multiple sensitizing factors can predispose to pancreatitis. Is it reasonable then to consider that any 1 patient could have more than 1 etiology as a cause of the pancreatitis? Prospective studies that standardize etiological classifications will, therefore, be important.

Regarding gallstone pancreatitis, what measures might reliably predict this etiology? Can an elevation in the alanine aminotransferase be used to identify children likely to have gallstone pancreatitis, as one may determine in an adult? What is the optimal feeding regimen for children with acute pancreatitis? What route of nutrition and type of diet is best? When or with what indicators should children be offered oral feedings?

Because severe acute pancreatitis is less common in children, multicenter prospective studies on the natural history of this disease are required to understand factors predicting disease severity and other complications. What happens to children with recurrent bouts of acute pancreatitis, or for that matter, those with idiopathic disease? Ultimately, it will be

important for the field to collect samples of blood, serum, and other components from patients with acute pancreatitis to link phenotype to genotype and biomarkers. A large, prospective, multicenter approach is clearly necessary to answer these critical questions.

CONCLUSIONS

Acute pancreatitis is a common problem in children that appears to be increasing in incidence. Standardized definitions of acute pancreatitis will be important as multicenter trials in children are considered. Biliary pancreatitis is the most common cause. Other treatable causes include medication-induced pancreatitis. Inciting agents should be withheld after a diagnosis is made. Roughly one-fifth to a third of the cases are idiopathic. About one fifth to one third will have recurrent pancreatitis. Management includes provision of adequate intravenous hydration, pain control, and nutrition. Finally, there is little known about the natural history of children with acute pancreatitis. Thus, prospective multicenter trials are needed to examine these issues.

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FIGURE 1.

Cellular pathways leading to pancreatic inflammation in pancreatitis. Experimental models of pancreatitis demonstrate that 1 or several insults can trigger pathological Ca²⁺ signals within the pancreatic acinar cell. Aberrant Ca²⁺ can cause intraacinar protease activation and the production of cytokines, recruitment of inflammatory cells, edema, and varying degrees of severity. Recovery and regeneration of the pancreas after injury may serve as an important target for therapy.

Major reports of AP in children, 1965–2010

TABLE 1

References *	Age range, y	Location	Patients, n	Most common etiologies			Clinical presentation, % presenting with the following symptom				Biochemical presentation, % with >3-fold elevation above ULN		Sensitivity of imaging modality for pancreatitis, %		Length of stay, days (range)	Mortality, %	Recurrence, %
				1st	2nd	3rd	Abdominal pain	Nausea or vomiting	Fever	Amylase	Lipase	U/S	CECT				
Park et al (11)	0–20	USA	215	Biliary	Medication	Idiopathic	90	73	—	50	73	29	60	—	Median 5 (3–10)	1.9	Overall, 15.3 (infants, 7.1)
Kandula and Lowe (14)	<3	USA	87	Systemic	Biliary	Infectious	—	—	40	—	—	51	47	—	Median 19.5 (2–129)	8	10
Nydegger et al (13)	0.2–15.9	Australia	279	Trauma	Idiopathic	Systemic	—	—	—	—	—	—	—	—	—	11.1	—
Sanchez-Ramirez et al (12)	—	Mexico	36	Idiopathic	Biliary	Systemic	95	86	27	86	87	—	—	—	Mean 25.7	0	34.5
Chen et al (23)	—	Taiwan	75	Idiopathic	Systemic	Biliary	94	64	33	—	—	57	74	—	—	5.3	21.3
Stringer et al (34)	4.0–16.0	UK	33	Biliary	Idiopathic	Medication	—	—	—	—	—	—	—	—	—	—	24.2
Werlin et al (9)	0–18	USA	180	Systemic	Biliary	Medications/idiopathic	68	53	—	83	82	24	54	—	Median 8; mean 24	6.1	12.2
Choi et al (25)	2.0–13.0	Korea	56	Medication	Biliary	Idiopathic	—	—	13	25	100	—	—	—	—	—	—
DeBanto et al (36)	0.1–16	USA	301	Idiopathic	Trauma	Biliary	—	—	—	—	—	—	—	—	—	—	—
Pezzilli et al (37)	2.0–17.0	Italy	30	Idiopathic	Infectious	Trauma	96	—	—	—	—	—	—	Median mild AP 13 (14–40); median severe AP 20 (6–51)	—	2	28
Tiao et al (22)	2.0–18.0	Taiwan	61	Trauma	Idiopathic	Systemic	95	38	30	84	90	79	34	—	—	1.6	14.8
Lopez (8)	—	USA	NA	Systemic	Trauma	Idiopathic	—	—	—	—	—	—	—	—	—	—	—
Weizman and Durie (18)	1–18.5	Canada	61	Systemic	Idiopathic	Trauma	100	70	30	—	—	25	—	—	—	21.3	—
Yeung et al (16)	2–18	Taiwan	43	Trauma	Systemic	Biliary	95	56	26	85	88	86	100	—	Mean 13 (2–90)	23	—
Haddock et al (17)	1–16	UK	49	—	—	—	80	80	—	85	—	71	—	—	—	—	—
Ziegler et al (19)	0.1–18	USA	49	—	—	—	82	53	12	—	—	—	—	—	—	—	—

References*	Age range, y	Location	Patients, n	Most common etiologies			Clinical presentation, % presenting with the following symptom				Biochemical presentation, % with >3-fold elevation above ULN		Sensitivity of imaging modality for pancreatitis, %		Length of stay, days (range)	Mortality, %	Recurrence, %
				1st	2nd	3rd	Abdominal pain	Nausea or vomiting	Fever	Amylase	Lipase	U/S	CECT				
Synn et al (25)	2–18	USA	48	—	—	—	—	—	—	—	71	—	—	—	—	—	—
Buntain et al (84)	2–18	USA	30	—	—	—	—	—	—	—	—	—	—	—	—	26.7	—
Jordan and Ament (20)	0–21	USA	54	—	—	—	67	44	—	—	—	—	—	—	—	—	—

AP = acute pancreatitis; CECT = contrast-enhanced computed tomography; ULN = upper limit of normal; u/s = ultrasound.

* Included only studies that had 30 or more children.

TABLE 2

Clinical presentation of acute pancreatitis in children

	Frequency (% of total cases)
Abdominal pain	80–95 (15–20)
Epigastric location	62–89 (15,21,22)
Back pain	<10 (9,17)
Radiation to the back	1.6–5.6 (19,20,22)
Diffuse	12–20 (15,19,20)
Guarding	29 (15) and 37 (17)
Nausea/vomiting	40–80 (9,12,16,18–24)
Abdominal distension	21–46 (15,16,18,19)
Grey Turner sign	2 (18)

TABLE 3**Reasons for false-positive amylase or lipase elevations**

Amylase (29)
Abdominal causes
Biliary tract disease
Intestinal obstruction/ischemia
Mesenteric infarction
Peptic ulcer
Appendicitis
Pancreatic cancer
Ruptured ectopic pregnancy
Prostate disease
Ovarian neoplasm
Afferent loop obstruction
Dissecting aortic aneurysm
Nonabdominal causes
Salivary gland
Salivary trauma
Infection (mumps)
Salivary duct obstruction
Irradiation
Thoracic
Myocardial infarction
Pulmonary embolism
Pneumonia
Metastatic lung cancer
Cardiopulmonary bypass
Metabolic
Diabetic ketoacidosis
Drugs
Opiates
Phenylbutazone
Trauma
Cerebral trauma
Burns
Renal disease
Renal insufficiency
Renal transplantation
Macroamylasemia
Lipase (30,31)
Pancreatic cancer
Nonpancreatic abdominal pain

Macrolipasemia
Renal insufficiency
Acute cholecystitis
Esophagitis
Hypertriglyceridemia

TABLE 4

Etiologies of acute pancreatitis in children

	Frequency (% of total cases)
Biliary	10–30 (9,11,12,14,16,18,22,23,34–36)
Medication	<25 (8,9,11,12,18,22,34,36,37)
Idiopathic	13–34 (8,9,11,13,14,18,22–24,34–37)
Multisystem disease	33 (9,12–14,18,23)
Trauma	10–40 (8,9,11–14,18,22–24,34–37)
Infections	<10 (8,9,11–13,18,22,34–36)
Metabolic	2–7 (9,11–13,18,34,36)
Hereditary	5–8 (9,11,13,14,18,36,37)