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Update to the Management of Pediatric Acute Pancreatitis: Highlighting Areas in Need of Research

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ABSTRACT

Acute pancreatitis is an emerging problem in pediatrics, with an incidence that is rising in the last 2 decades. Data regarding the optimal management and physician practice patterns are lacking. We present a literature review and updates on the management of pediatric pancreatitis. Prospective multicenter studies defining optimal management of pediatric pancreatitis are needed to guide care and improve outcomes for this patient population.

Key Words: acute pancreatitis, acute recurrent pancreatitis, chronic pancreatitis, pediatric

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Pancreatitis is an insult to the pancreas that leads to the presence of acute inflammatory cells, edema, and necrosis that may result in organ damage or fibrosis (1). In the majority of patients this inflammation is self-limited and reversible, leading to a 1-time acute pancreatitis (AP) episode. In some patients, AP progresses to acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP) (2). Patients with CP experience pain and possible pancreatic exocrine and/or endocrine insufficiency (3).

In the last 2 decades, an increased incidence of AP has been observed in the pediatric population (4). Although the cause is unclear, it may be explained by a heightened awareness of AP in children (5). Despite this more frequent presentation, data are lacking on the best diagnostic and management approaches to pediatric AP. The present management is extrapolated from adult studies and guidelines (6), in which the etiology is distinct. Biliary etiologies and alcohol play significant roles in adult AP (7,8), whereas pediatric cases are associated with different etiologies including biliary, metabolic, hereditary, and anatomic anomalies (2,4,9). Moreover, the natural history of progression from AP to ARP and CP is unknown. Only recently have consensus definitions for AP, ARP, and CP in pediatrics been published by the *I*nternational *S*tudy Group of *P*ediatric *P*ancreatitis: *I*n Search for a Cu*re* (INSPPIRE) (10). The overall lack of well-designed prospective studies represents a major obstacle to developing diagnostic and therapeutic guidelines for pediatric AP. In this void, it is likely that management of pediatric AP varies widely among practitioners, and offers an opportunity for standardization of care to improve outcomes for these patients.

In the present article we provide a framework to review the management of uncomplicated AP in pediatrics and identify areas for clinical research so that evidence-based guidelines for management of pediatric AP can eventually be developed.

DIAGNOSIS AND MONITORING OF AP

According to the Atlanta criteria and INSPPIRE definitions (10–13), a diagnosis of AP is achieved by meeting 2 of the following 3 elements: clinical symptoms, including abdominal pain, nausea, vomiting, or back pain; serum levels of pancreatic amylase and/or lipase $\geq$3 times the upper limit of normal; radiographic evidence of AP including pancreatic edema on ultrasound (US) or computed tomography (CT).

A detailed history to inquire about possible etiologies of AP should be obtained to allow appropriate management. Information obtained should include trauma history, gallstones, medications, viral infections, and other possible etiologies of AP (2).

Laboratory Testing

During an AP episode, pancreatic enzymes are released from the acinar cells into the circulation (14). When AP is suspected, serum and/or urinary pancreatic enzymes are evaluated. The most common tests are serum lipase and amylase. In 1 study, measurements of serum lipase had a sensitivity and specificity of 96.6% and 99.4%, respectively, whereas serum amylase had a sensitivity and specificity of 78.6% and 99.1%, respectively (15). Serum amylase has a shorter half-life and rises earlier than serum lipase, generally within hours of pancreatic injury (16). Based on its longer half-life, serum lipase is believed to be more useful in delayed presentations of AP, when the amylase levels may have already normalized. Thus, it is not uncommon to have normal serum amylase in AP, a phenomenon seen in approximately 20% of patients (17). Moreover, amylase may be normal in patients with AP and hyperlipidemia (18). In addition, findings of serum hyperamylasemia and hyperlipidemia are not limited to pancreatitis and can be reflective of other disorders including renal disease, intestinal inflammation, appendicitis, salivary gland disorders, or gynecological disease (19,20). Although other pancreatic enzymes have been described as markers of inflammation including carboxyl ester lipase, isoamylase, and phospholipase-A2 to diagnose pancreatitis (21), these enzymes have not been validated for common usage.

Other laboratories to be obtained during an attack are ones that would help identify the different etiologies or assess the severity of pancreatitis. These include calcium, triglycerides, transaminases, bilirubin, white blood cell count, urea nitrogen, and serum albumin (22). Directed therapy is important in patients when

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the etiology is clearly known, such as lowering the triglyceride level in hypertriglyceridemic pancreatitis (23).

Imaging Studies

Despite the present availability of advanced imaging modalities, abdominal US remains the first imaging study to be ordered in most patients with AP, including pediatric AP (9,24). US can be used to help confirm the clinical diagnosis of AP, and to assist in identifying underlying etiologies such as biliary pancreatitis. It is important to recognize the limitations of ultrasonography, specifically its lower sensitivity of approximately 70% in visualizing the pancreas in patients with AP compared with a sensitivity of >90% for CT scans (25,26). Abdominal CT is the second most common imaging modality used to diagnose and identify etiologies of pancreatitis (9,24). CT may be most helpful in patients with severe and complicated AP because it allows better visualization of masses, necrosis, and hemorrhage (27,28).

Although magnetic resonance cholangiopancreatography (MRCP) is seldom required for first attack of AP, it constitutes a valuable tool in the evaluation of pancreaticobiliary abnormalities. It has the advantages of not requiring ionizing radiation or the administration of iodinated contrast, and it provides high-quality multiplanar images of the pancreatic and biliary ductal systems. MRCP is useful in detecting intrahepatic and pancreatic ductal abnormalities, common bile duct abnormalities, choledocholithiasis, strictures, pancreas divisum, long common channel, and pancreatic and biliary tumors (29,30). Hence, MRCP has supplanted endoscopic retrograde cholangiopancreatography (ERCP) for diagnostic evaluation of the pancreaticobiliary system in many instances and has become the imaging study of choice to assess for ductal abnormalities. The use of MRCP during an episode of AP remains controversial because edema can obscure visualization of the ductal system (31). Intravenous secretin, a synthetic human hormone, increases the pressure of the sphincter of Oddi, leading to distention of the pancreatic ducts. It also has a role in detecting pancreatic divisum that may be missed in about one fourth of patients if an MRCP is performed without secretin (32). Literature on the use of secretin in MRCP is sparse in pediatrics. Although a few pediatric studies have shown improved visualization of the pancreatic duct by using secretin in MRCP (33,34), a recent study showed a small but significant increase in pancreatic and intrahepatic duct diameters, importantly, without a significant difference in overall image quality or duct visibility after the administration of secretin (35). In addition, MRCP with secretin may be used to assess duodenal filling and pancreatic duct compliance, as possible markers of abnormal exocrine pancreatic function—an area that needs further research in pediatrics (36).

Endoscopic US is yet another imaging study that may be considered in AP when there is no underlying cause identified by alternative modalities. The advantage of endoscopic US is the ability to obtain biopsies under direct visualization from lesions when indicated (37).

The authors recommend an US as the first-choice imaging modality and would reserve ordering of CT and/or MRCP for patients with complicated and severe pancreatitis.

Pain Management

Abdominal pain is the most common presenting symptom of AP. Pain management requires a careful balance between adequate control and oversedation. There are no data on optimal pain management in pediatric AP, and studies in adults have not identified a single superior medication. Morphine or related opioids were used in 94% of children with AP according to the INSPPIRE physicians' questionnaire (10). Despite concerns that morphine may cause sphincter of Oddi spasm and thus exacerbate AP, there are limited and conflicting data that the effect of morphine is significantly different from that of other opioids (38). Meperidine is used in adults but has the limitations of a shorter duration than morphine and the risk of neurotoxic metabolites with repeated dosing. Direct comparison of meperidine and morphine in AP is lacking.

More specialized pain management with celiac (39) and thoracic epidural analgesia (40) has been used effectively for AP pain in adults. The procedures do have associated risks (41), and their safety and efficacy have not been reported in pediatric AP. For patients requiring long-term use of narcotics, constipation is a well-recognized adverse effect. Recent studies in adults have found that μ-opioid antagonists methylnaltrexone (42) and alvimopan (43) improve opioid-induced dysmotility but have not been used routinely in pediatrics.

Narcotic-sparing medications including indomethacin have shown promise in pain management in AP (44). Newer medications including intravenous acetaminophen and ketorolac have also shown promise in reducing narcotic use following surgery in pediatric patients (45), and clinical trials of these narcotic-sparing medications in pediatric AP are warranted.

Intravenous Fluid Management

Supportive care in the management of uncomplicated AP, irrespective of etiology, continues to be the mainstay of therapy. Fluid resuscitation is an integral part of this care as evidenced by recently published guidelines (12,46). Unanswered questions remain as to the optimal components, timing, rate, and volume of fluid administration. The adult literature on the approach to optimal fluid resuscitation is limited, whereas comparative available pediatric data are grossly deficient. Most commonly, crystalloid solutions are the fluid of choice for intravenous fluid resuscitation (47). Recently, a randomized controlled trial on the use of lactated Ringer's solution versus normal saline in adult patients with AP found a reduction in the systemic inflammatory response syndrome presumably secondary to the greater pH-buffering capacity in lactated Ringer's solution (48). In line with efforts to favorably alter the course of AP, there is now supportive evidence for *early*, aggressive fluid resuscitation (47,49). ''Early resuscitation'' has been defined as receiving greater than one-third of the total 72-hour intravenous fluid volume within the first 24 hours of presenting to the emergency department (47). These findings emphasize the importance of first responders for patients with AP, starting with the emergency department providers, to implement early fluid management strategies, which may significantly affect the morbidity and/or mortality of patients with AP.

A small number of studies have concluded that aggressive fluid therapy may be associated with negative outcomes (50,51). In this context, it is worth mentioning that these studies had limitations of including only patients with severe pancreatitis (52), and in 1 the fluid therapy was predominantly given during the second 24-hour period (51). Despite these results, the intuitive value of fluid resuscitation based on objective measurements instead of a 1-size-fits-all approach seems logical and prospective studies are needed to define optimal fluid management in pediatric AP.

Nutrition

Nutrition has an important role in the management of AP through maintenance of the gut barrier function, inhibiting bacterial translocation and lowering the systemic inflammatory response (53,54). There are no published studies on the optimal timing of

nutritional intervention and mode of nutrition in pediatric pancreatitis. The data from adults are convincing that the earlier the nutrition is implemented, typically within 24 to 72 hours, the more favorable the outcomes and the lower the risk of progression into a multisystemic disease (55,56). According to recent meta-analyses, enteral nutrition was superior to total parenteral nutrition with a lower incidence of infection and multiorgan failure, resulting in lower mortality rates and a shorter hospital stay (57). To date, studies have shown that early enteral feeding via oral, nasogastric, or nasojejunal routes is safe and well tolerated in moderate and severe AP (58). A full general oral diet was tolerated in mild AP in adult patients and was not associated with abdominal pain relapse (59). In addition, there were no differences in outcomes between polymeric and elemental formulas and no evidence that immunoenhanced nutrients or probiotics are helpful in the management of AP (56). Optimal nutritional therapy in pediatrics should be further studied so that it can be uniformly applied.

Pharmacological Therapies

During the 350 years since Tulp first described AP (60), multiple attempts at medical therapies have failed to alter the course of the disease (61). More important, the latest meta-analyses have all concluded that initiation of antibiotics at presentation does not improve outcomes in adult AP and thus prophylactic antibiotic use is not recommended (62). A query of *www.ClinicalTrials.gov* identified a number of studies under way targeting the inflammatory response (dexamethasone, activated protein C, ulinastatin), pancreatic perfusion (pentoxifylline, localized low-molecular-weight heparin infusion, epidural anesthesia), and enteral supplements (glutamine, fish oil emulsions) in patients with AP. All clinical trials must overcome the fact that when targeting patients with predicted severe outcome early in the clinical course, it is likely that the inflammatory cascade has been triggered for a significant and variable period of time before treatment resulting in a heterogeneous population in which ''early intervention'' is a misnomer.

ERCP

Endoscopic therapy, specifically ERCP, should have a limited role in the management of AP. With the advancement in imaging modalities, ERCP is now used primarily as an interventional therapeutic tool in the care of both adults and children. In the setting of AP, ERCP is most helpful for gallstone pancreatitis in alleviating obstructive stones or sludge (63). According to the American Gastroenterology Association recommendations, urgent ERCP (within 24 hours) should be performed in gallstone pancreatitis with cholangitis, and early ERCP (within 72 hours) should be performed in patients who present with a high suspicion of a persistent common bile duct stone (64).

Gallstone pancreatitis usually needs to be managed by cholecystectomy or an ERCP before cholecystectomy (65,66). Data are lacking on the best management and timing of cholecystectomy for gallstone pancreatitis in pediatrics.

Pancreatic trauma is perhaps 1 unique diagnostic application of ERCP and has been used to define pancreatic ductal injury (67,68). In this setting, therapeutic intervention of pancreatic duct stenting to help resolve a peripancreatic fluid collection has also been safely and effectively applied (69).

Prognosis of Severity

There is no validated scoring system to predict severity in pediatric AP. Ranson criteria (70), the modified Glasgow scale (71), and the Apache II index (72) have been used to predict severity of adult AP, but all have limitations when applied to pediatrics (73,74). Newer, simplified scoring systems applied at time of admission have shown promise in adult AP (75,76). The first reported pediatric-specific severity score compared favorably with Ranson criteria and modified Glasgow scale with a higher sensitivity (67% vs 33% and 25%, respectively) but lower specificity (81% vs 93% and 90%, respectively) (77). This score requires 48 hours to complete, and it has not been validated in larger prospective studies. There are limited data on the use of CT scan for severity scoring in adults and pediatrics (78,79).

A single retrospective study in pediatric patients found elevated lipase >7 times upper limit of normal within the first 24 hours had an 85% sensitivity and 54% specificity for predicting severe AP (80).

A recent editorial that included a summary of the progress in AP scoring in pediatrics called for the need to develop a solid criteria to define severe pancreatitis and to form a scoring system that will predict the severe disease at presentation (81). Early identification of pediatric patients at risk for severe AP will continue to be a challenge without a prospectively validated scoring system for this population.

Further Testing, Genetic Mutation Analysis

The most common genes involved in pancreatitis are cationic trypsinogen (*PRSS1*) (82,83), the serine protease inhibitor Kazal type 1 (*SPINK1*) (84,85), the cystic fibrosis transmembrane regulator (*CFTR*) (86,87), chymotrypsin C (*CTRC*) (88,89), and calcium-sensing receptor (*CASR*) genes (90). Because of the fact that the majority of patients with AP do not have subsequent attacks in the future, assessing for genetic mutations should be reserved for patients with ARP or CP history.

CONCLUSIONS

Pediatric AP is diagnosed with increasing frequency, yet because of the lack of pediatric guidelines, management remains greatly variable. The present adult data support the use of intravenous fluids, early enteral nutrition, and pain management as the mainstays of therapy for uncomplicated AP but have not been validated in pediatrics. Well-designed prospective studies are needed in all areas of management of pediatric AP including the following:

1. Determine the optimal imaging modality for diagnosis of pediatric AP and validate advanced imaging techniques to assess pancreatic function in pediatrics.
2. Evaluate the use of narcotic-sparing medications in pediatric AP and the effect of standardized pain management on narcotic use, length of stay, tolerance of feeds, and complications.
3. Assess the safety and efficacy of weight-based rehydration strategies to identify the ideal intravenous fluid composition and rate of administration during initial management of pediatric AP.
4. Identify the optimal route and timing for introduction of enteral nutrition in pediatric AP.
5. Define the indications for and timing of surgical intervention for gallstone pancreatitis.
6. Prognostic scores: we need studies that could identify early markers for disease severity in pediatric AP. We need a robust and practical prognostic scoring system for pediatric AP.

Finally, the present review highlights the urgent need for prospective multicenter studies delineating optimal management of pediatric AP to develop evidence-based guidelines, improve patient outcomes, and hopefully alter the progression to ARP and CP.

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