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RISK FACTORS ASSOCIATED WITH BILIARY PANCREATITIS IN CHILDREN

A Thesis Submitted to the
Yale University School of Medicine
In Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

By

Michael Hong-Tak Ma

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RISK FACTORS ASSOCIATED WITH BILIARY PANCREATITIS IN CHILDREN.

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Little is known about risk factors for biliary pancreatitis in children. We hypothesized that ethnicity, obesity, and elevated pancreatic and hepatic biomarkers distinguish biliary from non-biliary and gallstone- from sludge-induced pancreatitis. We aimed to (1) characterize pediatric cases of biliary pancreatitis, (2) compare biliary with non-biliary cases, (3) examine differences between younger and older children, and (4) study features that distinguish gallstone- from sludge-induced pancreatitis.

We evaluated 76 episodes of biliary pancreatitis from 271 cases of acute pancreatitis in children admitted to Yale-New Haven hospital from 1994 to 2007. Of the 76 cases, 55% had gallstones, 21% had sludge, and 24% had structural defects. Hispanic children had a 2.85 ($p=0.01$) and 5.59 ($p=0.003$) higher probability of being diagnosed with biliary pancreatitis than white and black children, respectively. Median serum amylase and lipase in children with biliary pancreatitis were 64% and 49% higher, respectively, compared to other etiologies ($p<0.05$). In multiple logistic regression, aspartate aminotransferase (AST) was an independent predictor of biliary pancreatitis (OR=6.69, $p=0.001$). When comparing gallstone- with sludge-induced etiologies, obesity was an independent predictor (38% more prevalent, $p<0.01$) of gallstone cases.

Hispanic ethnicity was found to be a risk factor and AST a biomarker for biliary pancreatitis over other etiologies. Furthermore, obesity can distinguish gallstone- from sludge-induced pancreatitis. These findings may spur prospective studies to determine the optimal evaluation and management of children with biliary pancreatitis.

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LIST OF ABBREVIATIONS

AGA – American Gastroenterological Association

AST – Aspartate Aminotransferase

BMI – Body Mass Index

CBD – Common Bile Duct

CT – Computed Tomography

ED – Emergency Department

ERCP – Endoscopic Retrograde Cholangiopancreatography

GI – Gastroenterology

HELLP Syndrome - Hemolysis, Elevated Liver enzymes, Low platelets Syndrome

ICD-9 – International Classification of Disease, Ninth Revision

INSPPIRE – International Study Group of Pediatric Pancreatitis: In Search for a Cure

NAPS2 - North American Pancreatitis Study 2

NASH – Nonalcoholic Steatohepatitis

NPO – *Nil Per Os*

ULN – Upper Limit of Normal

US – Ultrasound

INTRODUCTION

Acute pancreatitis is a severe inflammatory disease of the pancreas, which accounts for over 210,000 hospitalizations annually.[1] In the United States, adult hospitalizations for acute pancreatitis are estimated to cost between $4.6 and $4.8 billion per year.[2] Both acute and chronic pancreatitis result in more than 31,000 deaths per year.[3] There are limited data in the literature on the clinical presentation, etiologies, and management of children with acute pancreatitis, all of which differ significantly from those of adults.

Biliary pancreatitis is a leading cause of acute pancreatitis in children, comprising 12 to 30% of all cases.[4] Although gallstones and other biliary diseases are common causes of acute pancreatitis in adults, very little is known about the presentation, risk factors, and outcomes of pediatric biliary pancreatitis or the features that distinguish it from other etiologies. Several studies have shown an increase in the incidence of acute pancreatitis in children during the past 20 years.[5-7] In a previously published report about our cohort, Park (2009) found a 53% increase in cases of acute pancreatitis between the period from 1995 to 2000 and the period from 2001 to 2006.[8] This finding was attributed to an increase in pediatric emergency department visits. As cases of biliary pancreatitis become more prevalent in children improved knowledge of risk factors will assist in its timely diagnosis and ensure that urgent endoscopic or surgical interventions can be implemented.[9]

In adults, biliary pancreatitis is primarily caused by gallstone obstruction of the common bile duct.[10] However, in children, biliary pancreatitis includes several etiologies including obstruction of the common bile duct (CBD) by gallstones, biliary

sludge or microlithiasis, choledochal cyst, and biliary tree anomalies.[8, 9] Predisposing factors for the development of gallstones include chronic hemolytic disease, obesity, cystic fibrosis, ileal resection, and chronic liver disease.[11] Over 70% of gallstones are pigmented bilirubin stones, while 15-20% are composed of cholesterol. Cholesterol stones are most common in obese children and pregnant adolescent girls. In contrast, sludge consists of calcium bilirubinate, cholesterol microcrystals and mucin, and may occasionally form gallstones. Biliary sludge often results from gallbladder stasis, such as with parenteral nutrition or during pregnancy.[12] In most cases, sludge is benign: it rarely causes symptoms and it disappears when the primary condition resolves. Nevertheless, sludge can develop into gallstones or even migrate and obstruct the common bile duct leading to biliary colic, cholangitis or pancreatitis.[13]

HYPOTHESES & SPECIFIC AIMS

In this study, we hypothesized that: (1) elevated pancreatic and hepatic biomarkers and ethnicity distinguish children with biliary pancreatitis from those with non-biliary pancreatitis; (2) obesity is a risk factor for gallstone pancreatitis; and (3) elevated pancreatic biomarkers and liver enzymes differentiate gallstone pancreatitis from sludge-induced pancreatitis.

We aimed to: (1) characterize the presentation of childhood biliary pancreatitis; (2) identify factors that distinguish children with biliary pancreatitis from those with other causes of pancreatitis; (3) compare biliary pancreatitis in younger and older children; and (4) examine differences between childhood gallstone- and sludge-induced pancreatitis.

PATHOPHYSIOLOGY OF ACUTE PANCREATITIS

Although pancreatitis has multiple etiologies, inflammation in acute pancreatitis is thought to be the result of a common pathway. The first step in the pathway occurs within the pancreatic acinar cells and consists of the production of aberrant nonphysiological calcium signals.[14, 15] The calcium signals activate intra-acinar pancreatic proenzymes, such as protease trypsin, leading to pancreatic acinar cell injury and the generation of cytokines.[16] The release of cytokines such as tumor necrosis factor-alpha results in an acute inflammatory response and extra-pancreatic inflammation.[16] This inflammatory response may cause pancreatic ischemia and in some instances result in pancreatitis.[17]

CHARACTERIZATION OF ACUTE PANCREATITIS IN CHILDREN

As mentioned earlier, our cohort has been previously described.[8, 14, 18] In order to more fully characterize our study cohort, we now present the important clinical findings from those studies.

In a study by Park (2009), the authors sought to characterize the etiologies of pediatric pancreatitis seen during that period. Of 271 cases of acute pancreatitis that met inclusion criteria, the mean age of the children was 13.1 ± 5.6 years and a recurrence rate of 15.3% was observed.[8] While 4 children (1.9%) died during hospitalization, only one patient death was attributable to complications of acute pancreatitis.

Acute pancreatitis was attributed to more than one etiology in 45 (21%) children. Biliary disease was found in 70 cases (32.6%) and was the most common etiology of acute pancreatitis in the cohort.[8] Medication-induced pancreatitis was found in 55 cases (25.6%) and was the second most common cause. Idiopathic causes, systemic

pathologies, trauma, and viral infections represented 44 cases (20%), 22 cases (10.2%), 20 cases (9.3%), and 17 cases (7.9%), respectively. Metabolic conditions, endoscopic retrograde cholangiopancreatography (ERCP), cystic fibrosis, and alcohol represented 11 cases (5.1%), 8 cases (3.7%), 4 cases (1.9%), and 2 cases (0.9%), respectively. Patients with trauma-induced pancreatitis included those with sports injury, motor vehicle accidents, child abuse, and accidental falls. Systemic causes were observed in critically ill patients and patients in the intensive care unit. Shock and/or sepsis were observed in 14 cases. The remaining systemic causes included HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) (1 case), systemic lupus erythematosus (1 case), acute liver failure (1 case), and active IBD (2 cases, 1 with ulcerative colitis and 1 with Crohn's disease). Metabolic conditions included diabetic ketoacidosis (5 cases), hypertriglyceridemia (3 cases), inborn error of metabolism (2 cases), and hypercalcemia (1 case). Propionic acidemia presented in both cases of inborn error of metabolism, one of which has been previously reported.[19] Comparative analysis of patients with idiopathic and non-idiopathic cases of pancreatitis showed no differences in age, sex, BMI, or weight-for-age values.

Acute pancreatitis was recurrent in thirty-three (15.4%) patients with an average of 2.7 episodes per child.[8] Compared with the 182 patients who had only a single episode of pancreatitis, a higher number of patients with recurrent pancreatitis were white (76%, 25 cases versus 48.9%, 87 cases; $P<0.05$). No significant differences in age, sex, etiology, BMI, or weight-for-age percentiles were observed. Gallstones, idiopathic causes, and medications represented the top three etiologies of the recurrent and single cases of acute pancreatitis.

Although a rise in childhood obesity has been well documented and a link between the severity of pancreatitis and obesity has been found in adults, the study by Park (2009) was the first to examine the role of BMI and the frequency of pancreatitis in children. Nearly 30% of children in the study were either overweight or obese, with BMIs at the 85th percentile or higher. This percentage is similar to the observed trends in Connecticut.[8, 19] However, a comparison of pancreatitis cases between the periods 1995 to 2000 and 2001 to 2006 showed no statistically significant difference in BMI percentiles. No differences in ethnicity were observed between the cohort and the general patient population seen at Yale-New Haven hospital or between the time periods. Finally, analysis of pancreatitis etiologies could not explain the increase in pancreatitis cases.

INCREASES IN THE FREQUENCY OF ACUTE PANCREATITIS IN CHILDREN

In Park (2009), the authors first sought to determine the frequency of pediatric pancreatitis at Yale-New Haven Children's Hospital during the 12-year period from August 1994 to July 2007.[8] Secondly, if indeed changes in frequency were observed, they aimed to analyze changes in etiologies, body mass index (BMI), and referral patterns in order to attribute potential causes for the observed trends.

The authors found that between the two 6-year time periods, cases of acute pancreatitis increased by 53.1% (16±3.35 cases/year from 1995 to 2000 versus 24.5±5.5 cases/year from 2001 to 2006; $P<0.02$).[8] No statistically significant differences were observed in patient demographics or BMI. Between these two time periods, there was a simultaneous rise in average pediatric emergency department (ED) visits (21,853±2120.6 visits/year to 27,856±1356.0 visits/year; $P<0.0004$). The percent increase in frequency of

acute pancreatitis cases decreased from 53.1% to 21.9% when normalized by annual pediatric ED visits and lost statistical significance (7.27±0.97 cases per 10,000 ED visits/year in 1995–2000 versus 8.86±2.3 cases per 10,000 ED visits/year in 2001–2006; P=0.16).

Greater clinical awareness and referral bias are two common causes of rising disease rates observed in retrospective studies. During the past twenty years in the United States there has been a national trend toward the regionalization of pediatric emergency care with an increase in referrals to tertiary care centers and children's hospitals.[20] In Park's (2009) study, the authors found that while pancreatitis cases rose by 53% between the 1995 to 2000 period and the 2001 to 2006 period, pediatric ED visits increased by more than 25%.[8] In order to assess the effect of referral patterns on the observed increase in pancreatitis cases, the incidence of pancreatitis was calculated by dividing the frequency by ED visits per annum. After this normalization, the observed increase in pancreatitis cases dropped by more than half, to 22%, and lost significance.

Several other studies have shown an increase in the frequency of pediatric acute pancreatitis and were conducted during similar time periods in Melbourne, Dallas, Wisconsin, and Mexico.[5, 7, 21, 22] However, since these studies did not report concurrent changes in ED visits, a comparison of results with Park's (2009) study was not possible. A study of 279 acute pediatric pancreatitis cases in Melbourne showed a significant increase of 27% in cases of pediatric acute pancreatitis from 1993 to 1997 and 1998 to 2002 (24.6 ±2.3 vs 31.2 ± 6 cases per year; P = 0.04), which was attributed to an increase in idiopathic and systemic-associated etiologies.

In addition to the limitations inherent in a retrospective study, in the study by Park (2009), a true incidence could not be calculated given that the pediatric population surrounding Yale-New Haven Hospital is shared with other referral centers, and as a result there is an overlap of catchment areas. Other limitations of the study include being based at a single center and that it consisted solely of mild cases of pancreatitis. Nevertheless, this study shows that over the last twenty years there has been an increase in cases of acute pancreatitis. It was also the first study to attribute this change to an increase in referral rates to tertiary care centers.

Differences Between Age Groups In Acute Pancreatitis

While the clinical practice and management of acute pancreatitis in children continues to advance, changes in management are largely based on adult studies. Several studies have investigated the incidence and etiology of pancreatitis in adults, however there are few studies pertaining to the diagnosis and treatment of acute pancreatitis in children.[5, 7, 8] In another study of our cohort, Park (2010) hypothesized that the clinical presentation and management of pediatric acute pancreatitis differed based on age.[18] In their analyses, the authors observed that infants and toddlers differed from adolescents in the level of serum amylase and lipase elevation, clinical presentation, length of hospitalization, type of radiographic evaluation, and mode of nutrition. A better understanding of the age-related differences in all these areas may assist in making earlier diagnosis, avoiding costly and unnecessary tests, and decreasing hospital length of stay and its associated medical costs. In this study, Park (2010) divided the 271 cases of acute pediatric pancreatitis into three age groups, infants and toddlers ages 0 to 2 years-old (14

cases, 12 patients), children ages 3 to 10 years-old (59 cases, 56 patients), and children 11 to 20 years-old (196 cases, 150 patients).

The authors found that the children in the 11 to 20 years-old age group had 11% more cases of recurrent pancreatitis than children in the 0 to 2 years-old and 3 to 10 years-old age group (18% versus 7.1%; $P<0.05$).[18] Three key presenting features of acute pancreatitis were examined including abdominal pain or irritability, epigastric tenderness, and nausea or vomiting. Abdominal pain or irritability was the most common feature, presenting in 91% of cases. Epigastric tenderness was found in 86% of cases while nausea or vomiting was the least common, presenting in 74% of cases. Ninety percent of cases presenting with abdominal pain met strict biochemical criteria, whereas 100% met biochemical criteria in cases diagnosed by additional criteria. These three key clinical features presented in fewer cases in the 0 to 2 years-old age group when compared to the older group (43% vs 93%; 29% vs 76%; and 57% vs 90%; for abdominal pain/irritability, epigastric pain, and nausea/vomiting, respectively; $P<0.05$ for all comparisons).

The biomarkers most commonly used in the diagnosis of pancreatitis are serum lipase and amylase.[3, 7, 23] In all age groups, serum lipase levels were found to be 5 times higher than amylase levels (24.1 times higher than the upper limit of normal (ULN) versus 4.4; $P<0.05$).[18] In the age group 0 to 2 years-old, serum lipase levels were >3 times ULN in all cases (100%) while serum amylase levels were >3 times ULN in 66% of cases ($P<0.05$). Serum lipase and amylase levels followed a similar trend in the other age groups, though the differences were not statistically significant. Cases of recurrent

pancreatitis had lower levels of serum lipase than those with a single episode (18.6 times ULN versus 27.9; P<0.05).

Radiographic imaging was widely used (82.6%) for the diagnosis of acute pancreatitis and the exploration of etiologies such as gallstones versus sludge.[18] The most frequently performed test was ultrasound (US), which was used twice as much as computed tomography (CT) scans (79.4% versus 41.9%; P<0.05). More than one radiographic modality was used in 38% of cases. Ultrasound and CT were both performed in 26.3% of cases and were the most commonly used radiographic combination. On US, gallstones and sludge were found in 53 cases (29.7%) and pancreatic parenchymal changes (edema or heterogeneity) were found in 51 cases (28.6%).

Examination of hospital management trends included the length of hospital stay, methods of nutrition, and the frequency of gastroenterology (GI) consultations. For the entire cohort, patients stayed a median length of 5 days (interquartile range [IQR], 3 to 10 days).[18] Children in the youngest group, ages 0 to 2, had longer hospital stays than the older groups (19.5 versus 4 days; P<0.05). Nutritionally, all patients were given intravenous fluids and appropriate pain control. Nearly 90% (240 cases) were made nil per os (NPO) at presentation. Patients were transitioned from NPO status to nutrition after an average of 2.1 days. Patients were transitioned to oral feedings, parenteral, and enteral nutrition in 65%, 22.3%, and 3.4% of cases, respectively. The youngest age group was less likely to be switched from NPO status to oral feedings than the older group (14.3% versus 67.1%; P<0.05). GI consultations were requested in 74% of cases.

Children ages 0 to 2 years-old were more likely to have a consultation than the older children (92% versus 73.3%; $P<0.05$).

In summary, 4 key differences emerged in the comparison between infants/toddlers and older children in this study.[18] First, the authors observed that infants/toddlers were less likely to present with classical signs and symptoms of acute pancreatitis. An elevated lipase level was more likely to lead to a diagnosis than amylase. Finally, the infants/toddlers had longer hospital stays and were more likely to be transitioned to parenteral and enteral nutrition than oral nutrition.

This study was the first to examine differences between younger and older children with acute pancreatitis. In an earlier study by Kandula (2008), they characterized a cohort of 87 infants/toddlers with acute pancreatitis at the Children's Hospital of Pittsburgh from 1995 to 2004.[23] When compared with the study by Park (2010), Kandula (2008) showed similar rates of abdominal pain or irritability: 46% of cases in the Kandula (2008) study and 43% in the Park (2010) study.[18, 23] However, more infants/toddlers (50% of cases) in the Kandula study had nausea/vomiting than in the Park (2010) study (29%). In spite of this difference, the key message in both studies is that compared with older children, infants/toddlers exhibit fewer clinical signs of pancreatitis at presentation and thus rely more heavily on other criteria for diagnosis. In contrast, the older group exhibited classic signs and symptoms of acute pancreatitis in greater than 70% of cases.

Similar to Park's (2010) study, Kandula (2008) also found that all infants/toddlers diagnosed with acute pancreatitis had elevated serum lipase levels greater than 3 times the ULN.[23] However, in the study by Park (2010), only 76% of older children had

lipase elevations greater than 3 times ULN; therefore, a diagnosis of acute pancreatitis necessitated other criteria in older children.[18] Park (2010) hypothesized that one reason for this finding is that serum lipase may be a more sensitive marker for pancreatitis in younger children. Alternatively, fewer infants/toddlers may have been diagnosed with acute pancreatitis using presenting clinical features or radiographic data, resulting in a bias towards a greater proportion of patients diagnosed using serum lipase elevation as criteria.

In both studies, the radiographic imaging modality most commonly used in the diagnosis of acute pancreatitis in infants/toddlers was US followed by CT.[18, 23] In addition, bivariate analysis in the Park (2010) study showed that a greater number of younger than older children underwent US. The clinical practice of using US as opposed to CT was likely due to a desire to minimize the long-term risks associated with ionizing radiation in young children.[24] In fact, the results of CT scans led directly to the diagnosis of acute pancreatitis in fewer than 60% of cases. This finding suggests that CT scans play a minimal role in the diagnosis of acute pancreatitis in children, especially infants/toddlers, due to its low sensitivity and concerns about radiation exposure.

Examination of the hospital management patterns revealed significant differences between infants/toddlers and older children and adults. Both studies showed similar lengths of hospital stay (median of 19.5 days in both).[18, 23] Interestingly, this was much longer than the 4-day median length of hospital stay observed in older children in the Park (2010) study and in adults with mild acute pancreatitis in a study by Jacobson (2007).[18, 25] Furthermore, infants/toddlers were more likely to be transitioned to parenteral or enteral nutrition than oral feedings and had higher rates of GI consultations

than older children. Park (2010) hypothesized that two reasons explain these important differences in management trends. First, complicated comorbid medical conditions associated with pancreatitis may be more common in infants and toddlers. In the Park (2010) study, two patients had propionic acidemia. This metabolic disorder necessitated longer hospital stays in order to stabilize their metabolic status, a more gradual transition to oral feedings with special diet, and the involvement of several subspecialty services, including GI. Secondly, care providers are inclined to treat infants/toddlers more conservatively given that pancreatitis is less common in this age group.

Park's (2010) study is important because it was the first to show key differences in the diagnosis and management of infants/toddlers and older children. The main messages presented by Park (2010) are that (1) care providers should have a lower threshold for suspecting pancreatitis in infants/toddlers given that they present with fewer typical symptoms than those seen in adults; (2) lipase is a better marker than amylase in making a diagnosis in this age group; and (3) US should be used more readily in order to confirm the diagnosis or to determine the cause of pancreatitis. As with the previous study of this cohort, this study suffers from the limitations present in all retrospective studies. In addition, it was based at a single center and all cases of pancreatitis were mild. Nevertheless, this study provides important insight into the presentation and management of infants/toddlers with pancreatitis. It also shows that not only are there differences between children and adults, but there are also significant differences between age groups among children with acute pancreatitis. Taken together, these findings may be useful in establishing guidelines and criteria for the diagnosis of acute pancreatitis in infants and toddlers.

DRUG-ASSOCIATED PANCREATITIS IN CHILDREN

After Park (2009) identified medications as the second most common cause (25.6% of cases) of pancreatitis, a study by Bai (2011) and the author of this thesis was conducted in order to ascertain which comorbidities and associated pancreatitis etiologies were found in children with drug-associated pancreatitis.[8, 14] Another aim of the study was to examine the hospital management of children with drug-associated pancreatitis and to determine the most commonly associated drugs among different age groups.

In this study, 55 cases (51 patients) of drug-associated pancreatitis were found.[14] Valproic acid, prednisone, and mesalamine were the medications most frequently associated with acute pancreatitis in the cohort and represented 13%, 12%, and 9% of all cases of drug-associated pancreatitis.

Comorbidities in cases with drug-associated pancreatities were two-fold more common than in cases of non-drug-associated cases (89% versus 39%; $P<0.0001$).[14] In the Bai (2011) study, the comorbidities most commonly associated with drug-associated pancreatitis were seizure disorders (20% of cases), acute lymphocytic leukemia (20%), and Crohn's disease (11%). Furthermore, another etiology of pancreatitis was attributed to nearly 33% of cases of drug-associated pancreatitis. These additional etiologies included systemic illness, biliary pancreatitis, structural defect of the pancreas, viral infection, hypertriglyceridemia, and cystic fibrosis, in order of decreasing prevalence.

In 2007, the American Gastroenterological Association (AGA) published a technical bulletin listing medications associated with pancreatitis.[26] In our cohort, 17 medications associated with pancreatitis were found. Categorizing our cohort based on the AGA classifications, 10 medications were in the "definite," 4 in the "probable," and 2

in the "possible" categories.[14] Of the drugs found to be associated with pancreatitis by the AGA, steroids were the most common drug association. Valproic acid, mesalamine, and trimethoprim/sulfamethoxazole were the next most common. Most cases had only one drug association (35 cases, 63.6%). However, 29% (16 cases) were associated with 2 drugs, and 7.3% (4 cases) had 3 or 4 drugs. In terms of demographic characteristics and clinical presentations between drug-associated and non-drug-associated cases, there were no statistical differences.

Ultrasound, CT, ERCP, and magnetic resonance cholangiopancreatography were the radiographic imaging modalities most commonly used. Compared to patients with non-drug-associated etiologies, patients with drug-associated pancreatitis underwent nearly double the number of CT scans (54.5% drug-associated cases versus 28.4% non-drug-associated cases; $P<0.0002$) and fewer ERCPs (1.8% versus 15.8%; $P<0.006$).[14] Median lengths of hospital stay were longer in the drug-associated group (10 days, IQR 4-19, versus 4 days, IQR 3-8; $P<0.0004$) and patients were 16.8% less likely to be transitioned to oral nutrition from an NPO status ($P<0.02$).

Interestingly, in drug-associated cases of pancreatitis, the use of valproic acid was higher in the younger age group (0 to 10 years) than the older age group (11 to 20 years) (29.4% versus 9.5% of cases).[14] This difference was larger when only considering cases of drug-associated pancreatitis with no additional etiology (45.5% in the younger group versus 9.8% in the older group).

In the Bai (2011) study, three important factors differentiating drug-associated pancreatitis from non-drug-associated etiologies were found.[14] CT scans were performed more often and ERCP performed less often in patients with drug-associated

pancreatitis compared to those with non-drug-associated etiologies. Patients with drug-associated pancreatitis also had longer hospital stays, and were more frequently transitioned to parenteral nutrition than oral nutrition after NPO status.

The Bai (2011) study was the first to examine drug-associated pancreatitis in children, though studies in adults have been previously published. In a retrospective study of 170 cases of pancreatitis, Vinklerova (2010) identified and compared 9 cases of drug-associated pancreatitis with the entire cohort.[27] The medication most commonly attributed to pancreatitis was found to be azathioprine. A study by Eland (1999) profiled 33 cases of drug-associated pancreatitis.[28] A retrospective study based on a questionnaire survey of 45 gastroenterology centers in Germany by Lankisch (1995) found that the incidence of drug-induced pancreatitis was 1.4%, in contrast to the 25.6% found in the Bai (2011) study.[14, 29, 30] The higher incidence of drug-associated pancreatitis in the Bai (2011) study may be due in part to the inclusion of cases that had both a drug-association and another concomitant pancreatitis etiology.

Bai (2011) examined concomitant comorbidities in children with drug-associated pancreatitis and found that seizure disorder, acute lymphocytic leukemia, and Crohn's disease were the three most prevalent comorbidities. Nearly half of these patients had either Crohn's disease or a hematologic abnormality.[14] The authors hypothesized that 2 factors may explain this finding. The presence of a cormorbidity may be a confounder since many drugs used to treat these disorders are themselves associated with drug-induced pancreatitis. For instance, the treatment of pediatric acute lymphocytic leukemia often consists of 6-mercaptopurine, corticosteroids, and L-asparaginase; and the

treatment of Crohn's consists of the two former drugs, both of which are associated with pancreatitis.

Another explanation may be that some comorbidities may be independent risk factors for pancreatitis. For instance, patients with Crohn's disease have higher risks of having anatomic abnormalities of the duodenum, developing gallstones, or innate immunologic dyscrasias.[31] Furthermore, Crohn's disease is associated with autoimmune pancreatitis type 2.[32] Bai's (2011) findings underscore the need for large cohort studies comparing pancreatitis risk using well-matched groups in order to distinguish whether drugs and comorbidities have additive or synergistic effects.

An intriguing finding was that younger children had a higher incidence of valproic acid-associated pancreatitis. One potential reason for this finding is that valproic acid is frequently used to treat absence seizures, a common childhood epileptic disorder.[33, 34] Therefore, the large number of valproic-induced pancreatitis cases may be attributed to the prevalent use of this medication in the treatment of childhood absence seizures. Another explanation for this finding may be that there are physiological differences in development between younger and older children making the former group more susceptible to medication-induced pancreatitis.

From 1968 to 1993, the World Health Organization found that out of 2749 reports of drug-associated acute pancreatitis, valproic acid was the most commonly associated drug and accounted for 8% (219) of cases.[33] Interestingly, 75% of all reported cases of valproic induced-pancreatitis occurred in children. Furthermore, a history of drug allergies presenting as rashes was found to be a risk factor for valproic acid-induced pancreatitis in a case series of 11 children.[35] In the same study, the length of treatment,

serum drug levels, and the concomitant use of other anti-epileptic drugs were not found to be risk factors. The key message from Bai's (2011) study is that valproic acid should be suspected as a potential cause of pancreatitis, particularly in young children.

Furthermore, Bai (2011) found that children with drug-associated pancreatitis had higher rates of CT scans and were transitioned to parenteral nutrition rather than oral feedings more often than children with non-drug-associated pancreatitis.[14] Given that patients with drug-associated pancreatitis had higher rates of comorbidities than patients with non-drug associated pancreatitis (89% versus 39%), one possible explanation for the more conservative management in this group is that they were perceived to be more ill.

In the Bai (2011) study, it was not possible to determine a causal relationship between medications and pancreatitis because it would have necessitated unethically rechallenging patients after stopping the medication.[14] The authors hypothesized that ascertainment bias toward increased cases may have resulted from increased routine or more prompt testing due to greater physician awareness of the associations of medications such as valproic acid with pancreatitis. Finally, referral bias may make drug-associated pancreatitis less relevant in non-tertiary care centers.

Bai's (2011) study exploring drug-associated pancreatitis underscores the importance of conducting a thorough patient history that fully examines the list of current medications. The medications linked to pancreatitis in both our study and the technical bulletin published by the AGA should be suspected as potential causes of pancreatitis in children.

BILIARY PANCREATITIS

Biliary tract disease refers to gallstones and sludge in the gallbladder and accounts for 10 to 30% of cases of acute pancreatitis in children.[4, 8, 21-23] In adults, gallstones and tumors alone are responsible for biliary obstruction and subsequently biliary pancreatitis. In contrast, 30% of cases of acute biliary pancreatitis in children are due to sludge.[8, 21, 23] Investigations examining why a greater proportion of children than adults with biliary pancreatitis have sludge revealed that abnormal liver function tests, specifically elevated transaminases and mild hyperbilirubinemia, were present.[9]

The removal of gallstones by ERCP is recommended if (1) the obstruction persists for 2 to 3 days, or (2) if cholangitis develops, or (3) if worsening pancreatitis develops.[4, 36-39] Cholecystectomy is advised after no more than 4 weeks in patients with cholelithiasis according to the AGA and within 2 weeks according to UK guidelines.[10, 38] The treatment of sludge is controversial and the use of cholerectic ursodeoxycholic acid in children has been previously reported.[40] It is unclear whether the biliary obstruction from sludge and pancreatitis resolved spontaneously or was a result of the medication.

PRESENT STUDY OF BILIARY PANCREATITIS IN CHILDREN

Our study will provide much needed data on how children with biliary pancreatitis present and their subsequent natural history. Therapeutic intervention is often required in acute biliary pancreatitis; therefore, the timely and accurate differentiation of biliary from non-biliary pancreatitis, and gallstone- from sludge-induced pancreatitis is clinically important. This information may help the pediatric gastroenterology community better understand how to diagnose and treat children with

biliary pancreatitis. Secondly, it will provide the basis for future large-scale studies of a prospective nature.

MATERIALS AND METHODS

STUDY GROUP AND INCLUSION CRITERIA

We evaluated 76 episodes of biliary pancreatitis occurring in 68 children from a database of 271 cases of acute pancreatitis in children of ages 0 to 20 years (224 children). These children were admitted to Yale-New Haven Children's Hospital in New Haven, Connecticut, between August 1994 and July 2007. We screened hospital admissions for cases of acute pancreatitis using International Classification of Disease, Ninth Revision (ICD-9) codes. All personal identifiers were removed in the database for the study. The institutional review board of Yale University School of Medicine approved the study protocol. Discussions of the overall cohort of patients, including etiologies, ethnic breakdown, referral trends for pancreatitis over time, and presentation and management trends, have been previously published by us and were discussed earlier in this thesis.[8, 18]

Inclusion criteria for acute pancreatitis in this cohort are as previously described.[8] Briefly, inclusion in the study group required that pediatric patients possess any 1 of the following 3 characteristics relevant to acute pancreatitis: (1) serum amylase or lipase higher than 3 times the ULN; (2) radiographic evidence demonstrating acute pancreatitis (minimum of changes in pancreatic parenchyma or peripancreatic fluid) on CT and US; (3) serum lipase increased more than 1.5 times the upper limit of normal (not a result of non-pancreatic causes of hyperlipasemia), along with the presence of 2 out of 3 clinical features—abdominal pain characteristic of acute pancreatitis, nausea or vomiting,

or epigastric tenderness. We modified the adult diagnostic guidelines published by the Acute Classification Working Group (1993) in establishing our inclusion criteria.[41] As it is difficult to consistently and accurately assess, we placed less emphasis on the presence of abdominal pain in children presenting with pancreatitis. To be considered a case of recurrent pancreatitis, a minimum of 4 weeks following the previous discharge needed to elapse. As previously reported, the overwhelming majority of patients (90%) met inclusion criteria (1) or (2).[8]

Of the 594 records (282 patients) identified by ICD-9 codes for acute pancreatitis, 323 records were excluded because they failed to meet inclusion criteria, had an incomplete chart record (46) or were cases of chronic pancreatitis (18). The latter was evidenced by calcifications observed on CT or the presence of chronic pancreatic duct abnormalities by ERCP.

In this study, the majority of children met inclusion via the first criteria (serum lipase and amylase; 180 children or 84%). Of these patients, 88% (155 children) had abdominal pain consistent with acute pancreatitis, and 84% (152 children) had 2 of 3 typical clinical characteristics of acute pancreatitis including nausea or vomiting, epigastric tenderness, and abdominal pain.[8]

DATA COLLECTION

The data collection and chart review were conducted by Dr. Alexander Park. Collected information included the etiology of pancreatitis, patient characteristics such as age, sex, ethnicity, and weight-for-age percentiles, biomarkers of pancreatitis (amylase, lipase, liver function tests), radiography, and hospital management. The etiology of pancreatitis assigned to each case was determined by the association reported in the chart

record. Biliary pancreatitis was defined as gallstone pancreatitis, biliary sludge or microlithiasis, pancreatic divisum, sphincter of Oddi dysfunction, and other/structural. A diagnosis of sludge-induced pancreatitis required radiographic evidence of (1) sludge in the gallbladder or CBD; (2) CBD dilatation; and (3) the absence of gallstones. Sphincter of Oddi dysfunction was diagnosed using Sphincter of Oddi manometry.[42] "Other/structural" biliary pancreatitis included cases in which an anatomic abnormality caused a disruption in normal pancreaticobiliary function. Non-biliary etiologies of pancreatitis included: medications, idiopathic, systemic illness, trauma, viral infection, a metabolic condition, ERCP, cystic fibrosis, and alcohol.

We stratified our cohort into three subsets. The first was a comparison between two groups within the entire cohort: non-biliary and biliary cases of pancreatitis. The second analysis evaluated differences between two age groups within the biliary subset: young children (0 to 10 years) and adolescents (11 to 20 years). The third was a comparison of two subsets of the biliary group: gallstone- and sludge-induced pancreatitis.

STATISTICAL ANALYSIS

Michael Ma performed all of the data and statistical analyses conducted in this thesis study. Continuous variables were analyzed using the Student's t-test and the Wilcoxon rank sum test for normally and non-normally distributed data, respectively. Comparisons of discrete variables were performed by chi-square and Fisher exact test. A p-value of <0.05 in bivariate analyses was considered statistically significant. Associations with a p-value <0.10 from the bivariate analyses were included in multiple logistic regression models. Non-normally distributed data were log-transformed prior to

conducting the adjusted analyses. Selection of important clinical predictors was performed using the backward step-wise approach. In the logistic regression models, variables with a p-value of <0.05 were considered significant independent predictors. Data were analyzed with SPSS 16 software (SPSS Inc., Chicago, IL). Age-adjusted percentiles for weight-for-age data were calculated using a program provided by the Centers for Disease Control (Atlanta, GA) and SAS (SAS Institute, Cary, NC).

The findings from this thesis research have been accepted for publication in the Journal of Pediatric Gastroenterology and Nutrition (October 12, 2011).[43]

RESULTS

ETIOLOGIES OF BILIARY PANCREATITIS

Biliary causes accounted for 28% of the 271 acute pancreatitis cases and represented the most common etiology in our study cohort. In 3% (2) of biliary cases, more than one other etiology was present. Gallstone- and sludge-induced pancreatitis accounted for most etiologies of biliary pancreatitis (55% and 21% of causes, respectively).

Other biliary etiologies included Sphincter of Oddi dysfunction (5%), pancreas divisum (5%), and other/structural causes (14%). The latter included pancreatic cyst or mass compressing the pancreatic duct, pancreatic duct stenosis, annular pancreas, and choledochal cyst. A direct comparison of these biliary etiologies was not conducted because the sample size was small.

Table 1. *Comparison of Cases of Biliary with Non-biliary Pancreatitis in Children*

	Biliary Cases=76	Non-biliary Cases=195	p-value
Characteristics			
Mean Age In Years (SD)	14.2 (5.1)	13.4 (5.6)	0.227
Female (% within group, n)	64.5 (49)	58.2 (113)	0.348
Ethnicity (%, n)			0.001^
White	48.0 (36)	64.6 (124)	
Black	17.3 (13)	20.8 (40)	
Hispanic	30.7 (23)	10.9 (21)	
Other	4.0 (3)	3.6 (7)	
Median weight-for-age percentile (IQR)*	77.7 (26.7-94.3)	56.8 (26.6-83.2)	0.069
>95 percentile (%, n)*	21.7 (15)	13.3 (24)	0.099
85-95 percentile (%, n)*	20.3 (14)	10.5 (19)	0.041^
0-85 percentile (%, n)*	58.0 (40)	76.2 (138)	0.004^
Signs & Symptoms (% within group, n)			
Abdominal Pain	94.7 (71)	93.0 (174)	0.785
Epigastric Tenderness	93.2 (69)	87.1 (162)	0.155
Nausea/Vomiting	73.0 (54)	78.4 (145)	0.352
Chemistries: Median (IQR)			
Amylase (-fold increase above ULN)	3.60 (1.29-8.73)	2.20 (1.29-4.67)	0.047†
Lipase (-fold increase above ULN)	14.67 (4.33-50.23)	9.87 (4.13-25.77)	0.036†
AST (mg/dL)	65.50 (23.00-147.25)	29.00 (18.00-45.00)	<0.001†
Total Bilirubin (mg/dL)	0.76 (0.40-2.96)	0.42 (0.26-0.68)	<0.001†
Calcium (mg/dL)**	9.56 (4.00)	10.43 (10.71)	0.554
Glucose (mg/dL)**	119.69 (50.64)	150.57 (187.03)	0.076
Radiology Performed (% within group, n)	92.1 (70)	79.5 (155)	0.013^
Modality (% of cases undergoing the following, n)			
US	84.3 (59)	80.6 (125)	0.513
CT scan	30.0 (21)	45.2 (70)	0.032^
MRCP	12.9 (9)	1.3 (2)	0.001††
ERCP	27.1 (19)	10.3 (16)	0.001^
Hospital Management Trends			
Median Length of Stay (n days, range)	5 (0-110)	4 (0-113)	0.229
GI Consult Ordered (% within group, n)	79.4 (58)	74.7 (142)	0.422
NPO at Admission (% within group, n)	95.9 (71)	91.4 (170)	0.204
Median Time to Nutrition after NPO (n days, range)	2 (0-7)	2 (0-9)	0.006†
Modality of Nutrition after NPO (% within group, n)			
Oral (PO)	70.4 (50)	72.4 (123)	0.761
Parenteral	28.2 (20)	22.9 (39)	0.390
Enteral	1.4 (1)	4.7 (8)	0.289

*Age-adjusted, **Calcium and Glucose was missing in 26.2% and 28.8% of cases, respectively.

^ Pearson chi-square test, †Wilcoxon rank sum test, ††Fisher's exact test

BILIARY VERSUS NON-BILIARY PANCREATITIS

There were 76 cases (68 children) of biliary and 195 cases (156 children) of non-biliary pancreatitis. In the biliary pancreatitis group, there were 17% fewer white children and a three-fold increase in Hispanic children than in the non-biliary group ($p=0.001$) (Table 1). We found that twice as many overweight children were in the biliary group ($p=0.04$).

In the biliary group, the median amylase and lipase levels were 3.6 and 14.7 times greater than ULN (Table 1). Children with biliary pancreatitis had serum levels of amylase, lipase, and aspartate aminotransferase (AST) that were 64% ($p=0.05$), 49% ($p=0.04$), and 225% ($p<0.001$) greater, respectively, than in children with non-biliary pancreatitis. Though an 80% higher median total bilirubin was seen in children with biliary pancreatitis ($p<0.001$), the total bilirubin levels were within normal limits in both groups. Therefore, this difference did not appear to be clinically relevant.

The majority of children with pancreatitis (83%) had radiographic imaging performed (Table 1). In the biliary group, 13% more children had radiographic tests performed ($p=0.01$). Of patients who underwent radiography, an ultrasound was the most commonly performed test with greater than 80% frequency in both biliary and non-biliary cases. CT scans were performed in 51% more children with non-biliary pancreatitis than with biliary pancreatitis ($p=0.03$). Examination of hospital management trends included length of hospital stay, rate of gastroenterology consultation, and method of nutrition after NPO status (oral or parenteral). There were no significant differences between the two groups in any of these parameters.

In the adjusted analysis, Hispanic ethnicity (p=0.01) and AST (p<0.001) were significant independent predictors of biliary pancreatitis (Table 2A). Hispanic children had a 2.85 (p=0.01) and 5.59 (p=0.003) higher probability for biliary pancreatitis than white and black children, respectively. Although the unadjusted association of weight-for-age percentiles with the outcome was significant, it was not found to be an independent predictor in the final model. This was explained by the finding that Hispanic children were more likely to be overweight than other children (p=0.03).

Table 2. *Multiple Logistic Regression Analyses.*

A. *Hispanic Ethnicity and AST: Risk Factors for Biliary Pancreatitis when Compared to Non-biliary Pancreatitis.*

Model	Variable	Odds Ratio (95% CI)	p-value
Full Model	Ethnicity		
	Hispanic (reference)	-	0.02
	White	0.36 (0.16, 0.81)	0.01
	Black	0.18 (0.06, 0.57)	0.00
	Other	0.67 (0.13, 3.43)	0.63
	Weight-for-age percentile	1.00 (0.99, 1.01)	0.75
	Amylase (fold increase above ULN)*	1.84 (0.75, 4.53)	0.19
	Lipase (fold increase above ULN)*	0.96 (0.46, 2.01)	0.92
	AST (mg/dL)*	6.71 (2.75, 16.35)	0.00
Reduced Model	Hispanic (reference)	-	0.01
	White	0.35 (0.16, 0.79)	0.01
	Black	0.179 (0.058, 0.552)	0.003
	Other	0.68 (0.13, 3.46)	0.64
	Amylase (fold increase above ULN)*	1.80 (0.88, 3.67)	0.107
	AST (mg/dL)*	6.694 (2.793, 16.046)	<0.001

B. *Weight-for-age Percentile: Risk Factor for Gallstone Pancreatitis when Compared to Sludge-induced Pancreatitis.*

Model	Variable	Odds Ratio (95% CI)	p-value
Full Model	Ethnicity		
	Hispanic (reference)	-	0.40
	White	0.44 (0.08, 2.29)	0.33
	Black	0.86 (0.61, 12.02)	0.91
	Other	0.08 (0.003, 1.96)	0.12
	Weight-for-age percentile	1.02 (1.00, 1.05)	0.05
	Amylase (fold increase above ULN)*	2.76 (0.45, 16.86)	0.27
	Lipase (fold increase above ULN)*	1.41 (0.39, 5.09)	0.60
Reduced Model	Weight-for-age percentile	1.02 (1.00, 1.04)	0.02
	Amylase (fold increase above ULN)*	3.25 (0.84, 12.7)	0.09

* Log-transformed

YOUNGER VERSUS OLDER CHILDREN WITH BILIARY PANCREATITIS

There were 15 cases (15 children) in the younger (0-10 year-olds) group and 61 cases (54 children) in the older (11-20 year-olds) group with biliary pancreatitis. The younger group comprised 20% of cases (Table 3). The most common etiologic category among younger cases was 'other/structural,' occurring with a 6-fold greater frequency than in older cases (p=0.001).

Table 3. *Comparison of Cases of Biliary Pancreatitis in Younger versus Older Children*

	Age Sub-Classification (yr)		p-Value
	0 to 10 Cases=15	*11 to 20* Cases=61	
Characteristics			
Mean Age in Years (SD)	5.8 (3.7)	16.3 (2.8)	-
Female (%, n)	53.3 (8)	67.2 (41)	0.314
Signs & Symptoms (% within group, n)			
Abdominal Pain	80.0 (12)	98.3 (59)	0.029†
Epigastric Tenderness	86.7 (13)	94.9 (56)	0.575
Nausea/Vomiting	53.3 (8)	78.0 (46)	0.100
Median weight-for-age percentile (IQR)*	83.9 (19.7-94.2)	69.7 (27.9-94.4)	0.914
>95 percentile (%, n)*	15.4 (2)	23.2 (13)	0.718
85-95 percentile (%, n)*	30.8 (4)	17.9 (10)	0.443
0-85 percentile (%, n)*	53.8 (7)	58.9 (33)	0.738
Etiologies (% within group, n)**			
Gallstone	31.3 (5)	57.8 (37)	0.057
Microlithiasis	25.0 (4)	21.9 (14)	0.745
Sphincter of Oddi dysfunction	0 (0)	6.3 (4)	0.700
Pancreas divisum	0 (0)	6.3 (4)	0.700
Other/Structural	43.7 (7)	7.8 (5)	0.001†

* Age-Adjusted, ** Several cases had multiple pancreatitis etiologies
† Fisher's Exact Test

GALLSTONE- VERSUS SLUDGE-INDUCED PANCREATITIS

There were 42 cases (40 children) of gallstone- and 16 cases (15 children) of sludge-induced pancreatitis. Cases of gallstone pancreatitis represented 72% of patients in this comparison group (Table 4). More than a third of children with gallstone pancreatitis were obese, while there were no such cases among those with sludge-induced

pancreatitis (p=0.01). No significant differences in age, ethnicity, abdominal pain, and nausea or vomiting were observed.

Analysis of serum biomarkers also showed significant differences between both groups (Table 4). Median lipase in the gallstone group was 30.2 times ULN and 2.3-fold higher than the sludge group (p=0.02). Similarly, median AST levels were nearly double the ULN and 84% higher than the sludge group (p=0.03). The median amylase level in the gallstone group was 4.80-fold higher than normal; and, although not statistically significant, there was a trend towards amylase levels being 90% greater than the sludge group (p=0.07).

Most children with gallstone and sludge-induced pancreatitis underwent radiographic imaging, with ultrasound as the most commonly performed test (Table 4). ERCP was only conducted in patients with gallstone pancreatitis (29% of gallstone cases, p=0.02). Hospital management trends differed significantly between the two groups. The median length of hospital stay in children with sludge-induced pancreatitis was 3 days longer than for children with gallstone pancreatitis (p=0.003). Conversely, the median time to starting oral or parenteral nutrition after acute NPO status in the sludge group was 2 days shorter than in the gallstone group (p=0.002). We also observed that 48% more children with sludge-induced pancreatitis were transitioned to parenteral nutrition (p=0.001), whereas 55% more children with gallstone pancreatitis began oral nutrition after NPO status (p<0.001). In addition, 53% more children with sludge-induced pancreatitis had comorbidities (e.g. leukemia, insulin-dependent diabetes mellitus, seizure disorders, asthma, and inflammatory bowel disease) than children in the gallstone group (p<0.001).

Table 4. *Comparison of Cases of Gallstone- with Sludge-Induced Pancreatitis in Children*

	Gallstone Cases=42	Sludge Cases=16	p-value
Characteristics			
Mean Age in Years (SD)	15.6 (3.6)	12.3 (6.0)	0.054
Female (% within group, n)	73.8 (31)	56.2 (9)	0.219
Ethnicity (%, n)			0.454
White	33.3 (14)	56.2 (9)	
Black	19.0 (8)	18.8 (3)	
Hispanic	45.2 (19)	18.8 (3)	
Other	2.4 (1)	6.2 (1)	
Median weight-for-age percentile (IQR)*	90.1 (46.6-98.4)	41.8 (16.3-90.8)	0.005†
>95 percentile (%, n)*	37.5 (15)	0 (0)	0.006††
85-95 percentile (%, n)*	20.0 (8)	28.6 (4)	0.485
0-85 percentile (%, n)*	42.5 (17)	71.4 (10)	0.062
Signs & Symptoms (% within group, n)			
Abdominal Pain	100.0 (42)	86.7 (13)	0.111
Epigastric Tenderness	100.0 (41)	80.0 (12)	0.023††
Nausea/Vomiting	81.0 (34)	60.0 (9)	0.161
Chemistries: Median (IQR)			
Amylase (-fold increase above ULN)	4.80 (1.76-12.93)	2.52 (1.25-4.77)	0.070
Lipase (-fold increase above ULN)	30.20 (7.21-102.00)	13.13 (4.10-14.73)	0.022†
AST (mg/dL)	90.00 (45.75-194.00)	49.00 (18.75-84.25)	0.034†
Total Bilirubin (mg/dL)	0.99 (0.45-3.80)	0.57 (0.42-2.20)	0.186
Calcium (mg/dL)**	9.91 (5.43)	8.94 (0.56)	0.498
Glucose (mg/dL)**	113.20 (33.08)	126.31 (49.51)	0.313
Radiology Performed (% within group, n)	97.6 (41)	93.8 (15)	1.000
Modality (% of cases undergoing the following, n)			
US	87.8 (36)	100.0 (15)	0.374
CT scan	26.8 (11)	33.3 (5)	0.741
MRCP	12.2 (5)	13.3 (2)	1.000
ERCP	29.3 (12)	0 (0)	0.024††
Hospital Management Trends			
Median Length of Stay (n days, range)	5 (0-85)	8 (3-100)	0.003†
GI Consult Ordered (% within group, n)	73.8 (31)	86.7 (13)	0.478
NPO at Admission, (% within group, n)	100 (42)	100 (14)	-
Median Time to Nutrition after NPO (n days, range)	3 (1-7)	1 (0-5)	0.002†
Modality of Nutrition after NPO, (% within group, n)			
Oral (PO)	83.3 (35)	28.6 (4)	<0.001††
Parenteral	16.7 (7)	64.3 (9)	0.001††
Enteral	0 (0)	7.1 (1)	0.560

*Age-adjusted, **Calcium and Glucose was missing in 20.68% and 25.86% of cases, respectively.
†Wilcoxon rank sum test, ††Fisher's exact test

In multiple logistic regression analysis, weight-for-age percentile was a significant independent predictor of gallstone pancreatitis in children (p=0.02) (Table 2B). Amylase, AST, and ethnicity were not found to be significant predictors of gallstone pancreatitis.

DISCUSSION

This study uniquely characterizes the presentation of 76 cases of biliary pancreatitis in children from a total cohort of 271 cases of acute pancreatitis. The main findings were that among children with acute pancreatitis, Hispanic ethnicity is a risk factor and an elevated serum AST level is a biomarker for a biliary etiology. Additionally, in children with gallstone- or sludge-induced pancreatitis, obesity is a risk factor for gallstone pancreatitis.

Biliary tract disease represented the plurality (28%) of our pancreatitis cases, consistent with previous reports which have shown that biliary tract disease accounts for one of the top three causes of acute pancreatitis in children.[9, 21, 23, 44-46] Since endoscopic or surgical intervention may be urgently needed in the management of acute biliary pancreatitis, it is critically important to examine risk factors that distinguish biliary from non-biliary pancreatitis.[9] The finding that Hispanic ethnicity is a risk factor for a biliary etiology may be explained by higher rates of biliary tract disease in this population group, perhaps due to a genetic predisposition or obesity.[47-49] We also observed that Hispanic children were disproportionately overweight compared to white and black children. In logistic regression analysis, however, we found that Hispanic ethnicity was independently associated with biliary pancreatitis, whereas obesity was not. Thus, a biliary cause should be suspected in Hispanic children with acute pancreatitis.

Serum amylase and lipase measurements are commonly used in the diagnosis of acute pancreatitis.[4, 18, 23, 29] We found that the height of amylase, lipase, and AST levels was significantly higher in children with biliary pancreatitis than with non-biliary pancreatitis. A similar result was observed in adults.[50] In adjusted analysis, AST was found to be a significant biomarker for biliary pancreatitis. Although AST is a hepatic enzyme, obstruction of the common bile duct, which may occur in biliary pancreatitis, can lead to hepatic injury and thus an increase in AST and alanine aminotransferase levels.[51] Our results confirm that a biliary cause should be suspected in children with acute pancreatitis who present with high levels of amylase, lipase, or AST. However, further studies validating an appropriate cut-off level are necessary.

The present study shows that gallstone pancreatitis is common, representing just over half (55%) of our acute biliary pancreatitis cases. Sludge-induced pancreatitis (21%) comprised the second most common biliary cause. To our knowledge, this is the first study to compare the presentation and management of gallstone with sludge-induced pancreatitis. We report that obesity is a significant independent risk factor for the diagnosis of gallstone pancreatitis in children with acute biliary pancreatitis. Although an odds ratio of 1.02 for weight-for-age percentiles appears low, the impact of this variable is sizeable. Our findings signify that for each unit increase in weight-for-age percentile, the probability of being diagnosed with gallstone pancreatitis over sludge increases by 2%. Therefore, compared to children of average weight-for-age (i.e. 50^{th} percentile), overweight children (i.e. 85-95^{th} percentile) have a 70-90% increased probability and obese children (i.e. 95-100^{th} percentile) have a 90-100% increased probability of presenting with gallstone pancreatitis over sludge. Our findings are in some ways

consistent with studies in adults, which demonstrate that obesity is a risk factor for the development of gallstones and for the severity of pancreatitis.[52-54] Thus, gallstone pancreatitis should be suspected in obese children with biliary pancreatitis.

In children with gallstone pancreatitis, the height of the lipase level was nearly double and AST was 86% higher than those with sludge-induced pancreatitis. A potential reason for this finding may be that, although biliary pancreatitis is associated with elevated hepatic enzyme levels, gallstones are more likely to cause a complete, albeit transient, obstruction of the CBD than sludge and thus lead to higher serum levels of AST. These biomarkers may be clinically useful in conjunction with radiographic imaging to differentiate gallstone- from sludge-induced pancreatitis.

A potential confounder in the interpretation of elevated transaminases as a biomarker of biliary pancreatitis is nonalcoholic steatohepatitis (NASH). In one study by Yener et al., 55% of adult patients with gallstones had associated NASH.[55] We know that obese patients are more likely to have NASH and more likely to have gallstone pancreatitis. However, at least by ultrasound, none of the children in our cohort had evidence of NASH or fatty liver.

Abdominal ultrasound was the most frequently used method of diagnostic imaging in all of our study groups, and it is one of the primary diagnostic studies used to evaluate gallstones and sludge.[56] However, due to constraints imposed by air and fluid-filled loops of bowel lying above the pancreas, the detection of gallstones in the CBD using abdominal ultrasound has a low sensitivity (50%) in patients with acute biliary pancreatitis.[57] Given the limitations of abdominal ultrasound, algorithms that incorporate risk factors, biomarkers, and diagnostic imaging may assist in the swift and

accurate diagnosis of acute biliary pancreatitis. The increased use of CT scans in cases of non-biliary pancreatitis is likely due to the need for further investigation in order to ascertain the definitive cause of pancreatitis.

Our findings that children with sludge-induced pancreatitis had longer hospital stays and were transitioned to parenteral nutrition more often than those with gallstone pancreatitis were likely due to higher observed rates of comorbidities in the former. Therefore, children with sludge-induced pancreatitis were more likely to be treated conservatively with parenteral nutrition, which is a known risk factor for sludge.[12]

In summary, elevated AST, lipase, and amylase levels may distinguish biliary pancreatitis from other etiologies. Hispanic children are more likely to be diagnosed with biliary pancreatitis. Finally, obesity as well as elevated levels of AST and lipase in children with biliary pancreatitis may be useful in distinguishing gallstone pancreatitis from sludge-induced cases.

The clinical presentation, epidemiology, and management of acute pancreatitis in children are poorly understood. Evidence-based diagnostic, prognostic, and treatment guidelines are urgently needed. Presently, pediatric gastroenterologists rely heavily on guidelines based on adult studies. This is problematic because multiple studies have shown that the etiologies, clinical presentation, disease course, and management of pediatric acute pancreatitis differ greatly from adults.

Since single-centers treat few children with acute pancreatitis, a multi-center approach to effectively and systematically characterize pancreatitis in children, establish diagnostic criteria, and provide treatment guidelines is necessary. A geographically diverse consortium comprised of nationally and internationally recognized

pancreatologists should be established to formalize standard definitions of acute pancreatitis and conduct evidence-based research. Multi-center studies with large samples of acute pediatric pancreatitis are necessary to shed light on the appropriate testing and optimal management of this disease, which is increasing in incidence.

The International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) is the first initiative to establish such a consortium (S. Husain, personal communication, January 10, 2012). The goals and objectives of this multi-center consortium parallel those of the North American Pancreatitis Study 2 (NAPS2), which is a multi-center effort evaluating adult patients with pancreatitis.[59] NAPS2's work has led to an improved understanding of the epidemiology, etiology, diagnosis, and management of pancreatitis in adult patients.

Though our findings require further validation in a multi-center, prospective study, taken together, they may be used in establishing a framework for diagnosing biliary pancreatitis in children. With earlier recognition of biliary pancreatitis and more accurate differentiation between gallstone- and sludge-induced pancreatitis, appropriate interventions including ERCP, ursodeoxycholic acid (in children with sludge), and/or cholecystectomy can be pursued more expeditiously, provide earlier relief of symptoms, and reduce the recurrence of pancreatitis.[58]

In addition to constraints inherent in a retrospective study, the limitations in our study are that all cases of pancreatitis were mild and based at a single center. Despite these limitations, to our knowledge, our study is the first to examine and distinguish the presentation and risk factors associated with gallstone versus sludge-induced pancreatitis in childhood. We hope that our findings will assist in the development of algorithms to

accurately diagnose and treat biliary pancreatitis. Furthermore, these data may facilitate the design of prospective studies to determine the optimal evaluation and management of children with biliary pancreatitis.

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