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Acute Pancreatitis in Childhood

A 10-Year Experience From A Thai University Surgical Center

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Objectives: This study aimed to describe etiology, management, and health outcomes of children developing acute pancreatitis at a tertiary Thailand pediatric surgery center.

Methods: Medical case records of all index cases during 2006–2016 were analyzed and reported.

Results: There were 42 male and 37 female patients, with a mean (standard deviation) age of 10.4 (4.5) years, included in the study. Medications were the commonest etiology for 39.3% of acute pancreatitis attacks, 11.4% for biliary tract disease cases, and 8% for postinterventional studies. In 30% of cases, no cause(s) was defined. Sixty-two patients (78.5%) had elevated serum lipase on hospital admission, whereas only 30.4% showed a raised amylase. Hospital stay was 15 days (interquartile range, 6–27 days). Two major complications in the series were pseudocysts (8.8%) and necrotizing pancreatitis (7.6%). Etiological factors and/or antibiotics were not directly linked to any specific complications. Seventeen children (22.8%) had 1 recurrent episode of acute pancreatitis documented. Mortality rate in index cases was 28%, with a higher percentage harboring a preexisting illness (34.4% vs 5.6%; $P = 0.01$) and in male than in female patients (41% vs 14%; $P = 0.01$).

Conclusions: Deaths from pediatric acute pancreatitis are more prevalent in male individuals and those with a preexisting illness. Targeted strategies aimed at “highest-risk” patients may potentially offset mortality.

Key Words: acute pancreatitis, pediatrics, lipase, amylase, pseudocyst, mortality

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In adults, acute pancreatitis is estimated to occur in 15 to 42 cases per 100,000 population per year and continues to rise inexorably by 2.7% each year.¹ Compared with adults, pediatric acute pancreatitis is considered much less common. However, it is strikingly notable that the incidence is now observed to be increasing to 1

to 13 per 100,000 population per year in the last decade or so, approaching rates of pancreatitis inflammatory disease comparable to those in adults.^{2–5} Although acute pancreatitis has perhaps a lower case fatality rate versus adults (5%–11% vs 21%–31%), progression of the disease to a severe form can be life-threatening.^{6–9}

The etiologic profile of acute pancreatitis is often very different from that observed in adults.¹⁰ According to the *International Study Group of Pediatric Pancreatitis: In Search for a Cure* (INSPPIRE), 2 of 3 criteria must be fulfilled to diagnose acute pancreatitis, notably, classical features of abdominal pain with serum amylase or lipase levels 3 times higher than the upper limit of normal value and radiology imaging typical of acute pancreatitis.^{5,11}

Management, risks stratification, and various severity scoring systems have been used to predict clinical outcomes in adults but have not been consistently or rigorously validated for specific use in children.^{12,13} Imaging modalities such as abdominal ultrasonography, computed tomography (CT) scans, and endoscopic retrograde cholangiopancreatography (ERCP) can readily identify biliary tract disease, which can then be followed with definite interventional and surgical management.¹⁴ However, acute pancreatitis may recur in 9% to 35% of children after a first acute attack.¹⁵ Strong correlations between acute recurrent pancreatitis in young patients and pancreatitis-related gene mutations have been proposed in many studies as a result of advanced knowledge in genetic research.¹⁶ This may lead therefore to modification of management strategies and pancreatitis prophylactic regimens in many expert centers.

Against this background, the current study aims to describe associations between the etiology of acute pancreatitis, management, and clinical outcomes linking factors associated with adverse events at a university faculty pediatric surgical center in Bangkok, Thailand.

MATERIALS AND METHODS

Medical chart records of all patients younger than 18 years with an index diagnosis of acute pancreatitis from January 2006 to December 2016 were examined. The *International Classification of Disease, Tenth Revision* diagnosis code for acute pancreatitis (K85) was used to screen all cases from the hospital administrative database. Patients who presented with recurrent episodes of pancreatitis (ie, chronic relapsing pancreatitis) during the study period and those having incomplete medical records were excluded from final analyses.

Demographic data, presenting symptoms, blood chemistry at diagnosis, and initial imaging findings were all recorded. Management of the acute hospital admission and treatment for complications were also collected. Severity of acute pancreatitis in this study was classified according to the North American Society of Pediatric Gastroenterology Hepatology and Nutrition Pancreas Committee into mild, moderate, and severe categories.¹⁷ Complications were defined as the development of pancreatic pseudocyst,

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necrotizing pancreatitis, or others. The final clinical outcomes were then noted as (i) complete recovery, (ii) development of complication(s), (iii) recurrence of pancreatitis, and (iv) death.

Statistical Analysis

Data were compared using the Student *t* test or Mann-Whitney test for continuous variables, and χ^2 or Fisher exact test for categorical variables. Correlation between etiology and age group was analyzed using phi-Cramér *V* statistic. All statistical analyses were performed with Stata version 14 (StataCorp LP, College Stations, Tex). Statistical significance was defined as a *P* value <0.05.

RESULTS

Demographic data are shown in Table 1. There were 79 patients (47% were female) in the study cohort with a median follow-up period of 40.8 months (interquartile range [IQR], 1.5–83.2 months). The mean (standard deviation [SD]) age at diagnosis was 10.4 (4.5) years, with 60% of patients older than 10 years. The average admission rate to our pediatric surgical center was 6 index cases per year. Hospital length of stay (LOS) was 15 days (IQR, 6–27 days). Patients having complications had a significant longer LOS (24 vs 12 days; *P* = 0.04).

Presenting Symptom and Laboratory Investigations

Abdominal pain was the most common presenting symptom occurring in 76% of cases. All patients had measurement of serum

lipase and amylase within the first 24 hours of hospital admission. We found that serum lipase was raised more than 3 times the upper limit of normal value range in 62 cases (79%), and elevated amylase was found in only 24 (30.4%) patients. Although 53 (67%) patients underwent radiology studies, 36 (46%) had imaging evidence of pancreatic inflammation at the primary diagnosis. Choledochal cyst and gallstones were noted in 8 of 53 (15.1%) and 2 of 53 (3.8%) cases, respectively, on initial imaging. Choledochal cyst was further confirmed with intraoperative cholangiography studies at the same institute. Two imaging modalities were deployed to aid diagnosis, notably, ultrasonography and CT scan. Twenty-two of 53 patients (41.5%) had surveillance follow-up imaging, which later revealed pancreatic pseudocyst in 7 patients (31.8%) and necrotizing pancreatitis in 6 cases (27.3%).

Etiological Factors

Medication agents were identified in 39.3% (31 of 79) of index cases, with 67.7% related to cancer chemotherapy. Pancreatic and/or biliary tract anomalies accounted for 11.4% acute pancreatitis episodes, whereas another 8% of patients sustained illness after surgical interventions, notably, ERCP (*n* = 3) and abdominal operations (*n* = 3). Gallstone pancreatitis, metabolic disorders, and trauma equally contributed to 2.5% of the patient cohort. Two patients had confirmed *SPINK1* gene mutations. The causes remained unidentified or unknown (ie, idiopathic) in 30% of cases (Fig. 1).

TABLE 1. Demographic Data: Pediatric Acute Pancreatitis Profiles Stratified by Complications

	Total (n = 79)	No Complications (n = 69)	Developed Complications (n = 10)	<i>P</i>
Sex, n (%)				
Male	42 (53.2)	35 (83.3)	7 (16.7)	0.25
Female	37 (46.8)	34 (91.9)	3 (8.1)	
Body weight, mean (SD), kg	33.8 (16.9)	33.6 (17.3)	35.2 (15.2)	0.77
Age at diagnosis, mean (SD), y	10.4 (4.5)	10.3 (4.5)	11.5 (4.2)	0.4
Symptoms, n (%)				0.50
Abdominal pain	60 (75.9)	52	8	
Abdominal distension	12 (15.2)	11	1	
Diarrhea	1 (1.3)	1	0	
Vomiting	1 (1.3)	1	0	
Asymptomatic	5 (6.3)	4	1	
Serum lipase, median (IQR), U/L	1853 (1101–6375)	1807 (1112–5690)	3607 (664–6914)	0.72
Serum lipase* \geq 900 U/L, n (%)	62 (78.5)	55 (79.1)	7 (70)	0.49
Serum amylase, median (IQR), U/L	244 (161–565)	240 (164–541)	364 (125–726)	0.75
Serum amylase [†] \geq 450, n (%)	24 (30.4)	21 (30.4)	3 (30)	0.98
Imaging at diagnosis, n (%)	53 (67.1)	44 (63.8)	9 (90)	0.15
Evidence of acute pancreatitis from imaging (n = 53)	36 (67.9)	28 (63.6)	8 (88.9)	0.24
Type of imaging at diagnosis (n = 53), n (%)				0.84
USG	26 (49.1)	22	4	
CT	26 (49.1)	21	5	
MRCP	1 (1.8)	1 (2.3)	0	
NPO, median (IQR), d	4 (2–8)	3 (2–7)	8 (5–25)	0.04
LOS, median (IQR), d	15 (6–27)	12 (6–3)	24 (15–95)	0.04

*Lipase reference range upper limit, 300 U/L.

[†]Amylase reference range upper limit, 150 U/L.

MRCP indicates magnetic resonance cholangiopancreatography; SD, standard deviation; USG, ultrasonography.

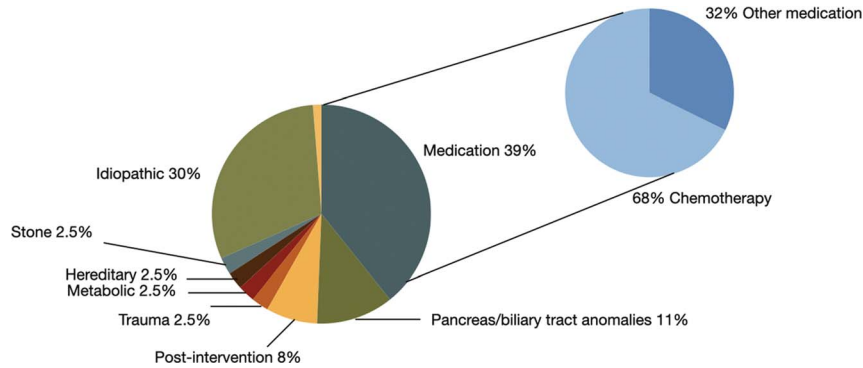


FIGURE 1. Etiology of acute pancreatitis.

We found that 3 of 6 children younger than 3 years (50%) had biliary tract anomalies, whereas only 4 of 27 children aged 3 to 10 years (15.4%) and 2 of 48 children 10 years or older (4.3%) had such pathology. Biliary tract anomalies were significantly related to acute pancreatitis in those children younger than 3 years ($r = 0.35, P < 0.01$). We further noted that 77.2% of patients had at least 1 identifiable comorbidity, of which hematologic malignancy was the most common co-association (37.7%). Immune-related disease disorders were recorded in 13 cases (21%; Fig. 2).

Management

All patients were hospitalized with acute admission. Apart from conservative management (ie, nasogastric tube, nil by mouth [NPO]/gut rest, intravenous fluid support, and analgesia), 53% of patients received intravenous antibiotics. The proposed drugs of choice here with good penetration to pancreatic tissue such as imipenem, clindamycin, piperacillin, fluoroquinolones, and metronidazole were prescribed in 29 of 42 cases (69%), whereas another 13 patients had other antimicrobial agents. The average pathological “third space” fluid losses were, on average, 27.7 mL/kg, with patients who later developed complications requiring more frequent fluid boluses during the first 48 hours of hospital admission versus those without complications; however, these differences were not statistically significant (33.4 vs 25.5 mL/kg, $P = 0.36$). Most patients (95%) had mild-grade acute pancreatitis, and the NPO time here was approximately 4 days (IQR, 2–8 days). Patients who developed pancreatitis-related complications had a longer NPO time (8 vs 3 days; $P = 0.01$) and hospital LOS (24 vs 12 days; $P = 0.04$).

Clinical Outcomes

We observed that 22.8% (18/79) of index cases had at least 1 recurrent episode of acute pancreatitis. Fifteen patients (15 of 18

[77.8%]) had imaging studies in the acute episodes of pancreatitis, which revealed 3 pancreatobiliary malformations, 1 metastatic pancreatic tumor obstructing the ductal system (primary site: orbital rhabdomyosarcoma), and 1 pancreatic divisum anomaly. Three of 18 patients did not undergo imaging in which the etiology of acute pancreatitis within this group was all medication related ($n = 2$) and post-ERCP ($n = 1$). In patients with acute recurrent pancreatitis, etiologies remained unidentified (ie, idiopathic in 5 of 18 cases [27.8%]).

Pancreatic pseudocyst was found to be the most common complication developing in 7 patients, and 3 patients needed drainage, notably, cystogastrostomy (2x) and cystojejunostomy (1x). Necrotizing pancreatitis occurred in 6 patients with necrosectomy and/or angioembolization to offset pancreatic hemorrhage performed in 3 cases. Factors associated with mortality are listed in Table 2. Fatalities occurred in 27.8% (22 of 79) of patients, of which 8 of 22 (36.4%) were in those cases who had disease progression and were transferred to our specialist center for compassionate/palliative care. A further 14 of 22 (63.6%) deaths in hospital were in patients with associated severe systemic disorders leading to multiorgan failure. Antibiotics usage according to their pharmacologic ability of tissue penetration was not associated with mortality (44.8% vs 23.1%; $P = 0.18$). Mortality rates were notably higher in male than in female patients (40.5% vs 13.5%; $P = 0.01$), patients with comorbidity disorders (34.4% vs 5.6%; $P = 0.01$), and in those receiving antibiotics (38.1% vs 16.2%; $P = 0.03$; Table 2).

DISCUSSION

Acute pancreatitis in the pediatric population is rare, although emerging data show a rise in incidence particularly in the past 2 decades.¹⁸ In this current study, the number of newly diagnosed cases of acute pancreatitis rose from 1 case per year in 2006 to an average of 6 cases annually in the following 10 years. The

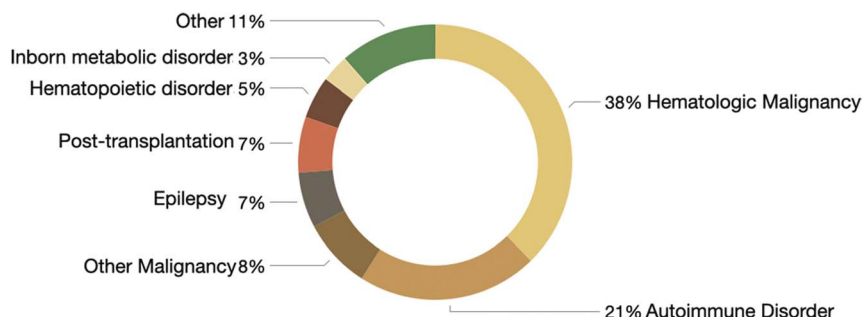


FIGURE 2. Comorbidity data.

TABLE 2. Factors Associated With Mortality

Data	Alive (n = 57)	Death (n = 22)	P
Sex, n (%)			0.01
Male	25 (59.5)	17 (40.5)	
Female	32 (86.5)	5 (13.5)	
Body weight, mean (SD), kg	35.3 (18.4)	29.7 (11.5)	0.19
Age at diagnosis, mean (SD), y	10.7 (4.8)	9.7 (3.5)	0.39
Comorbidity, n (%)			0.01
No	17 (94.4)	1 (5.6)	
Yes	40 (65.6)	22 (34.4)	
Laboratory result, median (IQR), U/L			
Lipase	1853 (1097–5690)	2842 (1112–6375)	0.89
Amylase	244 (157–642)	264 (173–502)	0.93
Antibiotics use, n (%)			0.03
No	31 (83.7)	6 (16.2)	
Yes	26 (61.9)	16 (38.1)	
NPO, median (IQR), d	3 (2–6)	8 (3–15)	<0.01
Types of antibiotics, n (%)			0.18
Group A	16 (55.2)	13 (44.8)	
Group B	10 (76.9)	3 (23.1)	
Developed complications, n (%)	6 (60)	4 (40)	0.45

Group A: antibiotics/antibiotics that are known to have adequate tissue penetration in infected pancreatitis; group B: antibiotics/other types of antibiotics.

increase in incidence may be linked to several factors including (i) increased awareness among clinicians, (ii) availability of diagnostic modalities, and (iii) better accessibility to specialist care at tertiary centers.^{7,19,20}

Bai et al⁷ and Suzuki et al¹⁰ suggested that the top 5 etiologies of acute pancreatitis are biliary tract disorders, medication, idiopathic causes, major systemic illness, and trauma, followed by infection, metabolic disease, and hereditary factors. Similar to our current findings, we also noted that medications, biliary tract anomalies, and intervention-related studies were the most common causes. Among adverse medication/drug reactions, acute pancreatitis is often “underscored” because of the difficulty in implicating a culprit drug. With increased awareness and identification of pharmacology agents associated with the etiology of acute pancreatitis, adverse medication/drug reactions have been more frequently reported.^{21,22} A further study demonstrated that congenital abnormalities of the pancreatobiliary system constitute a significant etiology of acute pancreatitis presenting in some 6.5% to 10.9% of all index cases of acute and chronic illness, respectively.²³ Congenital pancreatobiliary malformations contributed to 11.4% of acute pancreatitis in this current study, and this was most notable in the younger children. Hereditary pancreatitis has recently emerged as a contributing factor owing to advances in genetic testing. Although relatively rare, genetic disorders have provided major breakthroughs in our better understanding of acute and chronic pancreatitis including pancreatic cancer.²⁴ During the early period of the current study, full genomic sequencing was not available at our institute. With modern genetic testing detecting only *PRSS1* and *SPINK1* genes, 2 index cases with confirmed

SPINK1 gene mutations were identified. Some 27% of patients in our study were classified as having “idiopathic” or unidentified causes of acute pancreatitis. These findings reaffirm the results from earlier studies showing that idiopathic pancreatitis was attributed to some 13% to 34% of index cases.^{7,25,26}

The better sensitivity of elevation in serum lipase as an aid to timely diagnosis is likely a result of the degree of pancreatic insult and inflammatory response. Thus, to diagnose acute pancreatitis, a previous study concluded that serum lipase titer alone is sufficient. The co-ordering of both serum lipase and amylase has shown little to no increase in the diagnostic yield of illness.^{27,28} Taken together, here both serum lipase and amylase levels were not associated with severity of illness as defined by pancreatitis-related complications in our study. Furthermore, both enzymes had poor sensitivity and specificity to accurately predict prolonged LOS or mortality. Imaging is crucially needed to diagnose acute pancreatitis when the clinical setting is unclear in an effort to determine the underlying cause of pancreatitis, evaluate complications and disease severity, and to guide appropriate targeted intervention.²⁹ Ultrasonography is a convenient and noninvasive diagnostic test to diagnose acute pancreatitis and confirm potential causes such as choledochal cyst and screening for pancreatitis-related complications, notably, pseudocyst.¹⁰ However, recent studies demonstrate the higher sensitivity of CT and magnetic resonance imaging when compared with ultrasonography (78%–90% vs 52%–70%) and that these they are most likely beneficial in those patients with a complicated clinical course.^{7,27,30} We noted that 53 of 79 patients in our study had ultrasonography (67.1%) and/or CT scan (98%), whereas 68% had evidence of acute pancreatitis on initial imaging without the predictive ability to distinguish which patients would develop later complications ($P = 0.24$). Thoeni³¹ proposed that CT imaging is not indicated in patients who are clinically classified as having acute mild pancreatitis and show rapid improvement with appropriate medical management. The British Society of Gastroenterology guidelines recommend additional follow-up imaging in patients with clinical status deterioration or failure to show continued improvement.³² As study authors, we found that follow-up imaging mainly detected pancreatitis-related complications such as pseudocyst and necrotizing pancreatitis (a total of 10 of 53 patients who underwent radiologic investigation).

Most cases of acute pediatric pancreatitis are reportedly mild and resolve without complications.^{17,20} These factors therefore question the real benefit (if any) of using adult-defined acute pancreatitis scoring systems in the pediatric population.^{13,33,34} Lautz et al³⁵ reported multiorgan dysfunction or shock in greater than 2.8% of their patient population. In the current study, we noted a slightly higher “organ failure” rate of 5.1% during the first 24 hours of hospital admission, with more than half of our patients later making a recovery from illness within 48 hours without consequence. Common complications after acute pancreatitis such as pseudocyst formation have been widely reported in 10% to 23% index cases and necrotizing pancreatitis in $\leq 1\%$ of patients.^{36,37} Complicated illness accounts for prolonged NPO time and LOS within this cadre of patients. However, in our current study, we could not identify any predictive factors for patients acquiring pancreatitis-related complications. Fortunately, most complications can be safely managed conservatively.³⁸ Spontaneous resolution of pancreatic pseudocyst has been reported in 29% of cases. However, in certain conditions such as with infection, persistent abdominal pain, or hemorrhage, surgical drainage of the pseudocyst may be indicated.³⁹ Although necrotizing pancreatitis is associated with a high rate of mortality, it is mainly managed with aggressive supportive medical therapy including deployment of parenteral antibiotics.³⁶ Standard surgical treatments with such

disease course may include open pancreatic necrosectomy, with minimally invasive alternatives also proposed.⁴⁰

Prophylactic antibiotics are usually not indicated in mild illness because the incidence of infectious complications and mortality rates are considered low.¹⁰ Nevertheless, infectious sequelae are responsible for up to 80% of deaths in patients developing an illness. The health care medical team in our study had a lower threshold of prescribing antibiotic therapies in patients with associated comorbidities deemed prone to systemic infections and in those with malignancy, with autoimmune disease, or requiring immunosuppressive agents. We found in the present study that 21.4% of patients receiving antibiotics during hospital admission developed pancreatitis-related complication(s) and 38.1% of cases in this cohort died. Acute pancreatitis can feature as one of the crucial manifestations in systemic illness disorders and/or sepsis. The moribund state acquired in severe systemic illness can prolong starvation (nil po) and fasting and the tendency to deploy antibiotics with a higher risk of death in this vulnerable patient group. A 28% mortality occurred in our study cohort, but no deaths were directly attributable to acute pancreatitis.

Median LOS in hospital was 15 days, whereas Gay et al⁴¹ reported a median LOS of 4 days. Abu-El-Hajja et al⁴² recorded a LOS of only 3 days. The longer LOS in our hospital study population was likely a result of the varied primary systemic illness encountered in patients with underlying diseases even without a direct link or association with the rate of pancreatitis-related complications, recurrence, or mortality. Our study findings on sex and deaths (male vs female, 40.5% vs 13.5%; $P = 0.01$) is difficult to fully elaborate with biologic plausibility, but this may be related to different responses to infection or systemic inflammation between male and female patients. Further studies would be required to further confirm these associations.

The health care financial burden in treating acute pancreatitis is problematic in some countries, which has not been well reported before in Thailand.^{43,44} This study herein offers an opportunity to stimulate further collaborative nationwide research to identify hospital costs, inpatient admissions (including LOS), economic burden, and development of effective management guidelines for the future. The variation in etiologies for acute pancreatitis in this study herein reflects in part the retrospective nature of the report, which may also be complicated by referral bias of tertiary centers. A high volume (38%) of hematology-oncology patients considered “at risk” of developing acute pancreatitis with systemic deterioration also links to the high mortality rate in this current report. Better access to tertiary care facilities may allow personalized genetic testing and advanced imaging, which can aid reveal underlying etiology.

In closing, we have found a steady increase in the annual index case load of pediatric patients acquiring acute pancreatitis over a decade linked with this report. Initial imaging to accurately identify and define the precipitating causes may be useful, especially in younger patients in which the etiology of acute pancreatitis is more commonly discovered as compared with adults. Finally, better management and monitoring of acute pancreatic illness in specific pediatric at-risk groups, notably, those with preexisting diseases, may also potentially improve patient survival.

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