Acute Pancreatitis in Children: Neither to be Underestimated Nor to be Overlooked

Çocuklarda Akut Pankreatit: Ne Hafife Alınmalı, Ne de Gözden Kaçırılmalı

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ABSTRACT

Objective: Despite varying presentations of acute pancreatitis (AP) in children, the diagnosis has been increasing in recent years due to increased awareness. We aimed to identify the relationship among etiology, presentation symptoms, treatment response and complications of the children with acute pancreatitis.

Material and Methods: Thirty children diagnosed with AP were evaluated for clinical and laboratory findings, treatment approaches, complications in the tertiary children hospital retrospectively.

Results: The mean age of the patients was 12.4 ± 4.3 years and 60% were male. The drugs (30%), biliary tract diseases (26.7%), infections (16.7%), hyperlipidemia (10%) were the main causes of AP, in 10% of patients no etiological factor was detected. Abdominal pain (83.3%), nausea (70%), loss of appetite (63.3%), vomiting (56.7%), and fever (20%) were the most common symptoms. Ultrasonography, abdominal tomography and magnetic resonance cholangiopancreatography revealed pancreatitis related changes 63.3%, 85%, 70% of patients, respectively. Oral feeding was started on median 4 days (1-30), with polymeric diet (30%), and medium chain triglyceride rich enteral diet (70%). The median length of hospitalization (LOH) was 16.5 days (4-66). The patients fed with polymeric diet had a shorter hospitalization duration ($p<0.036$). The delayed initiation of oral feeding caused longer LOH ($p<0.001$).

Conclusion: Consequently, this study underlines the children with acute abdominal pain, especially who use drugs like asparaginase and valproic acid, or that are known to have gallstone/biliary sludge, need to be examined for acute pancreatitis through pancreatic enzymes and ultrasonography. Moreover, the study also highlights that early feeding in acute pancreatitis is related with shorter hospitalization duration.

Key Words: Acute Pancreatitis, Children, Etiology, Treatment

ÖZ

Amaç: Çocuklarda akut pankreatitin (AP) farklı prezentasyonlarına rağmen, farkındalığın artması nedeniyle son yıllarda tanısı artmaktadır. Bu çalışmada akut pankreatitli çocuklarda etiyoloji, başvuru semptomları, tedavi yanıtı ve komplikasyonlar arasındaki ilişkiyi belirlemeyi amaçladık.

Gereç ve Yöntemler: Üçüncü basamak çocuk hastanesinde AP tanısı alan 30 çocuk klinik ve laboratuvar bulguları, tedavi yaklaşımları, komplikasyonlar açısından retrospektif olarak değerlendirildi.

Bulgular: Hastaların yaş ortalaması 12.4±4.3 yıldı ve %60'ı erkekti. İlaçlar (%30), safra yolu hastalıkları (%26.7), enfeksiyonlar (%16.7), hiperlipidemi (%10) AP'nin ana nedenleriydi, hastaların %10'unda etiyolojik faktör saptanmadı. Karın ağrısı (%83.3), bulantı (%70), iştahsızlık (%63.3), kusma (%56.7) ve ateş (%20) en sık görülen semptomlardı.

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Ultrasonografi, abdominal tomografi ve manyetik rezonans kolanjiyopankreatografi hastaların sırasıyla %63.3, %85, %70'inde pankreatitle ilişkili değişiklikler olduğunu gösterdi. Oral beslenme ortanca 4 günde (1-30), polimerik diyet (%30) ve orta zincirli trigliseritten zengin enteral diyet (%70) ile başlatıldı. Ortanca hastanede yatış süresi (LOH) 16.5 gündü (4-66). Polimerik diyetle beslenen hastaların hastanede yatış süresi daha kısaydı (p<0.036). Oral beslenmeye geç başlanması daha uzun LOH ile ilişkili olduğu saptandı (p<0.001).

Sonuç: Sonuç olarak, bu çalışma akut karın ağrısı olan, özellikle asparajinaz ve valproik asit gibi ilaçlar kullanan veya safra taşı/safra çamuru olduğu bilinen çocukların pankreas enzimleri ve ultrasonografi ile akut pankreatit açısından incelenmesi gerektiğinin altını çizmektedir. Çalışma ayrıca, akut pankreatitte erken beslenmenin daha kısa hastanede yatış süresi ile ilişkili olduğunu vurgulamaktadır.

Anahtar Sözcükler: Akut Pankreatit, Çocuklar, Etiyoloji, Tedavi

INTRODUCTION

Inflammation of pancreas is defined as acute pancreatitis (AP). Acute pancreatitis generally presents with an abrupt stomachache. The pancreas enzymes are elevated, and specific findings are detected in imaging studies (1-2). The most frequently observed causes of AP in children are biliary and systemic diseases, drugs, and trauma (2-6). Despite the disease's typically mild course in children, severe, systemic involvement and even death are also reported. The primary symptom is abdominal pain, occurring in 80-95% of cases. In younger children, irritability may also be observed (2,7,8). Nausea and vomiting are the second leading symptoms, occurring with or without severe abdominal pain. The diagnosis of AP has increased among children due to the increase in awareness (3-6). However, despite increased diagnostic capacity, lack of knowledge about the epidemiology, most common underlying causes, established diagnostic criteria, imaging techniques, appropriate management strategies and complications of AP persists. This lack of knowledge often leads to delay in diagnosing and treating AP (7, 9,10).

There are few publications focusing on AP in children. We aimed to examine the demographic and clinical characteristics, laboratory and imaging findings, treatment modalities, complications, mortality, and morbidity rates of pediatric patients with acute AP who treated in our center.

MATERIALS and METHODS

A comprehensive retrospective examination was conducted on the medical files pertaining to the pediatric AP cases in University of Health Science Ankara Training and Research Hospital. This entailed a thorough analysis of the initial admission reports of clinical, laboratory, and imaging tests, as well as the treatment administered. The results were recorded in a dedicated form, based on the data extracted from the patient files. The diagnosis of the patients was made by the researchers who primarily conducted the study.

According to INSPPIRE (11), the International Study Group of Pediatric Pancreatitis: In Search for a Cure, diagnosing acute pancreatitis (AP) in children involves meeting at least two of the following three criteria:

1. Typical abdominal pain,
2. Serum amylase and/or lipase levels at least three times the upper limit of normal (ULN)
3. Imaging studies showing characteristic findings of AP.

Patients with recurrent attacks of acute pancreatitis and chronic pancreatitis were excluded. Approval for the study was received from the education board of Ankara Child Health and Diseases Training and Research Hospital (08/06/2012-126).

The demographic and clinical features, treatment procedure, complications, length of hospitalization (LOH), morbidity and mortality rates were recorded. Additionally, complete blood count (CBC), biochemical parameters including serum electrolytes, hepatic enzymes, renal function tests, lipid profile, serum amylase, lipase, pancreatic amylase, acute phase reactants (like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)), prothrombin time, partial thromboplastin time were recorded according to age (12). Furthermore, specific investigations for the etiology, imaging procedures including ultrasonography (USG), computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) were also evaluated.

The LOH was compared with the type of oral nutrition (polymeric diet or medium chain triglyceride (MCT) and whether the patient received total parenteral nutrition (TPN)).

Patients' anthropometric measurements were recorded at initial date of hospitalization. A patient was classified as having short stature if the height-for-age z-score was below -2. A patient was classified as underweight if the weight-for-age z-score was less than -2. The classification of body mass index (BMI) percentiles according to sex and age is as follows: underweight is defined as a BMI below 5%, overweight as a BMI between 85% and 95%, and obesity as a BMI above 95% (13).

If no etiological cause could be identified based on history, laboratory tests, and imaging methods, these patients were classified as "idiopathic AP". The following conditions were included as the category of "biliary disease related AP": gallstones, biliary sludge, annular pancreas, choledochal cyst, and other biliary tract disorders. Acute pancreatitis in patients who had used drugs, and if the condition resolved when the drugs were discontinued was defined as "Drug-related pancreatitis" (7).

For the statistical analysis, patients were separated into two groups (mild or severe AP), based on the criteria outlined by Atlanta, DeBanto, Acute Physiology and Chronic Health

Evaluation II, Ranson, and Modified Glasgow. In recent years the Pancreas Committee of the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) criteria was used to further classify acute pancreatitis as mild, moderately severe, or severe acute pancreatitis (4,14-18).

IBM Statistical Package for the Social Sciences, version 21.0 (SPSS Inc., Armonk, NY, IBM Corp., USA) was used for the statistical analysis. The Kolmogorov-Smirnov test was utilized to determine the conformity of variables to a normal distribution. Continuous variables were analyzed using the mean, standard deviation or median (minimum-maximum) and categorical variables using frequency and percentage for descriptive statistics. The student's t-test was used to assess the significance of differences between groups in terms of mean values, while the Mann-Whitney U test for the differences between median values. The Chi-Square test was performed for the analysis of categorical variables. $p<0.050$ was accepted as statistically significant.

RESULTS

There were 30 children with a diagnosis of AP, male patients consisted of 60% (n=18). The mean age of these patients was 12.4 ± 4.3 years, with a range of 3 to 18 years. Comparison of gender of patients due to mean age did not show any significance [girls 11.1±4.9 years (range: 3-17 years), boys 13.3±3.8 years (range: 6-18 years), p=0.176].

The most common presenting symptom was abdominal pain at the initial admission to the hospital, occurring in 83.3% of cases (n=25). In 13 patients (52%) it was located in the epigastric region and in 8 patients (32%) it radiated to the back. The symptoms on admission to hospital is shown in Figure 1.

Drugs were the most common causes of AP in the study population. L-asparaginase was the most frequently identified drug involved in the development of AP. The etiological factors responsible for AP are listed in Table I.

A total of 15 (50%) patients exhibited concurrent medical conditions. These were in the order of frequency: acute leukemia

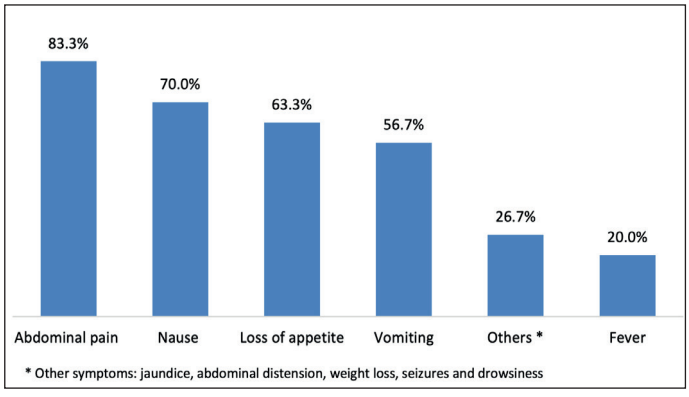

Figure 1: Symptoms of patients

Table I: Causes of acute pancreatitis

Etiology	n (%)
Drugs	9 (30)
L-Asparaginase	4 (13.3)
Valproic acid	2(6.7)
Imipramine hydrochloride	1 (3.3)
Mesalazine	1 (3.3)
Carbamazepine	1 (3.3)
Biliary diseases	8 (26.7)
Gallstone/biliary sludge	6 (20.1)
Choledochal cyst	1 (3.3)
Annular pancreas	1 (3.3)
Infection	5 (16.7)
Mumps	2 (6.7)
Brucella	1 (3.3)
Hepatitis A	1 (3.3)
Ebstein Barr Virus	1 (3.3)
Hyperlipidemia	3 (10)
Idiopathic	3 (10)
Cystic fibrosis	1 (3.3)
Secondary to ERCP	1 (3.3)

ERCP: *Endoscopic Retrograde Cholangiopancreatography*

(n=6, 20%), epilepsy (n=4, 13.3%), hereditary spherocytosis (n=1, 3.3%), hyperlipidemia (n=2, 6.7%), Crohn's disease (n=1, 3.3%), and chronic renal failure (n=1, 3.3%).

A review of the family history revealed that 6 (20%) of the parents were first-degree relatives. In addition, one patient's father (3.3%) had a prior diagnosis of AP, although the cause was unknown.

After examination of anthropometric measures, we determined that 13 patients (43.4%) had short stature, 11 (36.7%) exhibited wasting, 13 (43.4%) were underweight, 3 (10%) were classified as overweight, and 2 (6.7%) were obese.

A total of five patients (16.7%) exhibited a fever (>38°C), while one patient (3.3%) demonstrated decreased systolic blood pressure, tachycardia, and tachypnea in accordance with age-specific norms. The physical examination findings revealed the following: abdominal tenderness (n=18, 60%), hepatomegaly (n=6, 20%), splenomegaly (n=5, 16.7%), abdominal distension (n=4, 13.4%), icterus (n=4, 13.4%), and rebound tenderness (n=2, 6.7%).

Serum amylase and lipase levels increased to three times of the upper limit of normal (ULN) level in 86.6% (26/30) and 73.9% (17/23) of the patients, during the follow-up respectively. Four (17.3%) patients had normal amylase levels despite elevated lipase levels. The median amylase levels were 586 U/L (250-2658), representing a fivefold increase above the ULN levels. The median lipase levels were 305 U/L (23-2922), exhibiting a six-and-a-threefold increase above the ULN levels.

Table II presents a comparative analysis of demographic and laboratory findings between patients with biliary disease and non-biliary disease, as well as between patients with drug-induced and non-drug-induced acute pancreatitis. In AP patient

Table II. Demographic and laboratory findings of the patients with acute pancreatitis

	Biliary group (n=8)	Non-biliary group (n=22)	p	Drug-induced group (n=9)	Not drug induce group (n= 21)	p
Female*	3 (37.5)	9 (40.9)	0.723	4 (44.4)	8 (38.1)	0.214
Age (years)†	12.9±4.3 (3-16)	12.2±4.4 (5-18)	1.000	10.9±5.3 (5-18)	13±3.7 (3-18)	1.000
Amylase (U/L)‡	1106 (413-2569)	504.5 (250-2658)	0.021	405 (270-908)	596 (250-2658)	0.164
Lipase (U/L)‡	184 (61-2922)	322.5 (23-2868)	-	292 (23-980)	450 (61-2922)	0.643
ALT (U/L)‡	199.5 (66-468)	15.4 (1-521)	<0.001	14 (1-67)	75 (1-521)	0.019
AST (U/L)‡	113 (28-519)	25.5 (10-1662)	<0.001	26 (15-30)	35 (10-1662)	0.070
GGT (U/L)‡	232 (108-1317)	18.5 (2-548)	<0.001	21 (7-349)	93 (2-1317)	0.263
T. bil (mg/dl)‡	1.9 (0.4-34.6)	0.5 (0.1-4.0)	0.004	0.4 (0.1-1.3)	1.0(0.2-34.6)	0.007
D. bil (mg/dl)‡	0.9 (0.1-26.4)	0.2 (0-3.0)	<0.001	0.1 (0.02-0.4)	0.3 (0-26.4)	0.012
LOH (day)‡	13 (7-40)	17 (4-66)	0.597	18 (6-66)	16 (4-40)	0.533

***:** *n(%) Fisher's Exact Chi-Square test,* **†:** *mean±SD (minimum-maximum) Student's t test,* **‡:** *Median (min-max) Mann Whitney U test,* ***Amylase:** *Pancreatic amylase,* ***ALT:** *Alanine aminotransaminase,* ***AST:** *Aspartate aminotransferase,* ***GGT:** *Gamma-Glutamyl Transferase,* ***T.bil:** *total bilirubin,* ***D.bil:** *direct bilirubin,* ***LOH:** *The length of hospitalization*

Table III. Imaging findings in acute pancreatitis

	Ultrasonography (n=30)	Computed tomography (n=20)	MRCP(n=10)
Enlarged pancreas*	18 (60)	14 (70)	5 (50)
Hypoechoic pancreas*	13 (43.4)	12 (60)	3 (30)
Dilated pancreatic duct*	3 (10)	2 (10)	2 (20)
Peripancreatic fluid*	3 (10)	4 (20)	2 (20)
Pseudocyst*	2 (6.7)	2 (10)	1 (10)
Stones or sludge*	11 (36.7)	3 (15)	4 (40)

***:** *n(%),* ***MRCP:** *Magnetic resonance cholangiopancreatography*

Table IV: Severity of acute pancreatitis

	Number of patients (%)	
	Mild pancreatitis	Severe pancreatitis
Atlanta Criteria	27 (90)	3 (10)
De Banto Criteria	28 (93.3)	2 (6.7)
Ranson and Modified Glasgow Criteria	28 (93.3)	2 (6.7)
Acute Physiology and Chronic Health Evaluation II Criteria	30 (100)	-
North American Society of Pediatric Gastroenterology, Hepatology and Nutrition	26 (86.7)	4* (13.3)

***:** *Moderately severe*

group related to biliary disease, median amylase, ALT, AST, GGT, total and direct bilirubin levels were significantly increased (p= 0.021, p<0.001, p<0.001, p<0.001, p=0.004, p<0.001 respectively). The patients with drug-induced pancreatitis had lower ALT, total and direct bilirubin levels than other causes (p= 0.019, p<0.007, p<0.012 respectively).

The USG showed a normal pancreas in 4 (13.4%) or couldn't be assessed in 7 patients (23.4%) because abnormal gas was present. In four of the seven patients, CT scans revealed an enlarged pancreas, decreased echogenicity, or a heterogeneous pancreatic appearance. Of the patients 63.3% had changes on USG, whereas 85% on CT and 70% on MRCP respectively. Radiologic findings were absent in three patients. The findings from the imaging studies are summarized in Table III. The severity of AP is demonstrated in Table IV based on the criteria outlined in the methods.

Treatments administered to the patients included intravenous fluid resuscitation and cessation of oral feeding. Twenty-eight (93.3%) patients received gastroprotective treatment.

A nasogastric tube was placed in twenty-five patients (83.3%) for gastric secretion drainage. Three (10%) patients received paracetamol treatment, and six (20%) patients needed meperidine treatment to relieve their abdominal pain. Oral feeding was initiated on median four days (range: 1-30 days) [Polymeric diet (n=9, 30%), MCT diet (n=21, 70%)]. The LOH time of those fed with polymeric diet [median: 8 days (range: 4-34 days)] was significantly shorter than those fed with MCT diet [median: 18 days (range: 4-66 days)] (p=0.036). Oral feeding was started in a median of five days (range: 1-30 days) with polymeric diet, while in three days (range: 2-9 days) with MCT diet.

Total parenteral nutrition was given to six (20%) patients on 4±2.5 days of hospitalization and continued for 20±15.9 days. Median LOH time of the TPN receiving patients [37 days (range: 18-66 days)] was significantly longer than others [13

days (range: 4-40 days)] ($p<0.001$). A delayed initiation of oral feeding was related with long LOH time ($p<0.001$).

The mean time for amylase levels to normalize was 9.1±4.6 days, while lipase levels normalized in 11.7±6.9 days.

The complications observed included the formation of pseudocysts in two patients on the 9th and 32nd days of hospitalization, respectively. The previous case was resolved spontaneously, whereas in the latter case, drainage was required. Other complications were noted, including two cases of sepsis (6.7%), as well as one instance of severe electrolyte disturbance. A third patient, who had AP related to hypertriglyceridemia, developed pancreatic necrosis on the 15th day of hospitalization.

There was no mortality attributable to AP. Although the acute pancreatitis was resolved, two patients (6.7%) died because of their underlying systemic disease.

Recurrent pancreatitis was seen in four patients (13.4%) and the number of episodes ranged between two and four. No patient exhibited the evolution of chronic pancreatitis, nor did any patient demonstrate pancreatic insufficiency during the follow-up.

DISCUSSION

Acute pancreatitis is a painful inflammatory condition that leads to significant complications. Over the past 10-15 years, the incidence of acute AP in children has increased due to awareness of the disease and improved access to laboratory and radiologic evaluation (3,5). Abdominal pain, nausea, and vomiting are among the most frequent symptoms in AP patients. The pain is generally in the epigastric region, radiating to the back (3).

Werlin et al. (19), reported that abdominal pain, mostly localized to epigastrium was the leading symptom (67.7%), followed by vomiting (44.8%). Pain radiated to the back was reported to be 9.6% of the children with abdominal pain. Deveci et al. (20) noted that the most frequent complaints at first visit were abdominal pain (94.4%), vomiting (60.2%), malnutrition (36.1%), nausea (17.6%), diarrhea (13%), and fever (13%). Similarly, abdominal pain was also the most common symptom in our study (83.3%), with almost half of the cases localized in the epigastric region and 32% and radiated to the back. Nausea (70%) was the second common symptom and other symptoms were as follows: loss of appetite (63.3%), abdominal tenderness (60%), vomiting (56.7%) and distension (13.4%).

The diagnosis of AP was mainly based on the elevation of pancreatic enzymes. Especially in the first 24 hours after the onset of symptoms, the increase of amylase is more valuable in diagnosis of AP. Lipase is a more specific diagnostic indicator and remains elevated longer than amylase (1). Chlebowczyk et al. (21), reported that amylase values were ≥3 times higher than normal in 63 (82.9%) of 76 acute pancreatitis attacks in 51 children. Lipase values were examined in 28 of these patients and it was determined that lipase values were ≥3 times higher than normal in 19 of them. In our study, serum amylase was increased in 86.6% and lipase levels was raised in 73.9% of patients. The difference may be because of the fact that serum lipase wasn't measured in all our patients.

The etiology of AP differs in various studies (1). Trauma, medication, systemic diseases, biliary diseases, and infections are at the forefront etiologic factors in children (1, 4). Salim et al. (22), stated that the most common causes of AP were medication (31.2%) gall stone (9%), and idiopathic (32.8%). Sweeny et al. (23), reported the most common etiology as idiopathic (31%), drug use (23%), biliary or gallstones (18%), and viral infection or systemic diseases (17%). In our study, the most common etiologies were drugs (30%), biliary diseases (26.7%) and infections (16.7%). As the patients with trauma related AP are hospitalized in pediatric surgery division, there was no traumatic AP in our study.

Drug history should be carefully questioned in patients with AP because too many drugs have been reported to cause AP. Valproic acid, L-asparaginase, 6 mercaptopurine/azathioprine, corticosteroids and mesalamine have been noted as the most common causes of AP in children (3,24).

The incidence of AP during L-asparaginase treatment ranges from 2 to 18% and repeated doses are reported to increase the risk (25). In our study, L-asparaginase was the most common drug in patients with drug-induced pancreatitis. This may be attributed to the fact that our hospital is a referral center for the treatment and follow-up of children with leukemia.

Valproic acid was the most common drug that led to AP, which may be related to the frequent use in childhood epilepsy due to Werlin et al's study (19). In our study valproic acid was the second most common drug which led to AP.

Gallstones, microlithiasis, bile sludge, sphincter of Oddi dysfunction, pancreatic division, and structural/other abnormalities (choledochal cyst, annular pancreas, mass, or cyst compressing the pancreatic duct) constitute the common biliary causes of childhood pancreatitis (3). Similarly, in our study, biliary causes gallstones and sludge were 75% of biliary causes.

According to Choi BH et al. (26) , serum lipase, ALT, AST, and total bilirubin levels were elevated in the biliary group compared to the non-biliary group. Similarly, our study showed that the biliary group had significantly elevated median levels of amylase, ALT, AST, GGT, and total and direct bilirubin compared to the non-biliary group. Serum ALT, total and direct bilirubin levels of drug-related AP were found to be statistically significantly lower than group that is no drug related due to our findings. This

significant difference may be due to inclusion of biliary causes in the non-drug group.

Suvak et al. (27) diagnosed AP secondary to brucellosis in 21 patients among 347 acute brucellosis patients. In our study, a blood culture obtained from the patient who was hospitalized for abdominal pain, vomiting, and fever revealed Brucella infection. In countries like ours where Brucella infection is endemic, brucella-associated AP should be considered when suspected by history and clinic.

The treatment of AP is based on nutrition significantly. It was believed that stopping oral feeding in patients with AP reduced pancreatic secretion 20 years ago. However, early feeding has been shown to reduce pancreatic complications in large, controlled studies (3). In patients with mild pancreatitis, oral nutrition is recommended for the first 24-48 hours (28). The median time to initiate oral feeding in our study was four days (1-30 days). Without enteral nutrition or postpone initiation of enteral nutrition due to the severe course of AP may end with the atrophy of the gastrointestinal tract and increased complications from bacterial translocation. This fact may explain the longer LOH time with delayed initiation of oral feeding. The cases of mild pancreatitis had shorter duration of hospitalization in which a full solid diet was started in the initial treatment (29). In our study, the median hospitalization time was shorter in initially fed with a polymeric formula [8 days (4-34)] compared to MCT-enriched peptide-based formula [18 days (4-66)] (p=0.036). This may be due to a preference for the MCT-enriched peptide-based formula in clinically more severe cases of AP.

CONCLUSION

Acute pancreatitis, although infrequent in childhood, is a critical health problem. Children with abdominal pain, especially those on medications such as L-asparaginase and valproic acid or those with a history of gallstones or biliary sludge, should be evaluated for acute pancreatitis through pancreatic enzyme testing and ultrasonography. The study also suggests that early initiation of nutrition in acute pancreatitis is associated with a shorter hospitalization period.

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