Diplomarbeit

Pancreatitis in childhood: Assessment of the need for surgical therapy

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unter der Anleitung von

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Graz, am…….. (Unterschrift)

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Zusammenfassung

Hintergrund: Pankreatitis im Kindesalter ist eine seltene Erkrankung, die im Gegensatz zu den Erwachsenen viele verschiedene Ursachen haben kann und eine spezifische Behandlung erfordern kann. Ziel dieser Studie war es, die Gründe für eine chirurgische Behandlung der Kinder mit Pankreatitis zu erforschen.

Methoden: In dieser retrospektiven Studie aus dem Zeitraum 1991 - 2010 wurden die gesamten klinischen Daten von Kindern im Alter von 1 bis 18 Jahren, die wegen Pankreatitis an der Universitätsklinik für Kinder- und Jugenchirurgie in Graz behandelt wurden; ausgewertet. Bei der Datenerfassung wurden die Entlassungsdiagnosendie Aufenthaltsdauer, das Alter bei der Erstdiagnose der Pankreatitis, das Geschlecht, die Laborwerte, die radiologischen Untersuchungen, die Ätiologie, die Therapien, und das Outcome, ausgewertet. Eine Follow-up Untersuchung wurde im Median 7 Jahre und 11 Monate (1 bis 20 Jahre) nach der Operation durchgeführt.

Ergebnisse: 82 Kinder (46 Jungen, 36 Mädchen) wurden während des Studienzeitraumes behandelt. Das mittlere Alter bei Erstdiagnose war 10.7 ± 4.5 Jahre. 67 Kinder (82%) wurden wegen einer einzelnen Episode der akuten Pankreatitis behandelt, 3 Kinder hatten eine akutrezidivierende Pankreatitis und 12 Kinder (15%) litten unter einer chronischen Pankreatitis. Die eingesetzten bildgebenden Verfahren beinhalteten: Ultraschall (100%), Computertomografie (43%), Magnetresonanztomografie (23%), Magnetresonanz-Cholangiopankreatikoographie (23%) und Endoskopisch Retrograde Cholangiopankreatikographie (18%). Der Mittelwert des höchsten Wertes der Serumlipase betrug 4531.4 U/l (-205), und der Serumamylase 938.3 U/l (-100). Die Ursachen der Pankreatitis waren Trauma (33%), Gallenwegserkrankungen (26%), sekundär zu anderen Erkrankungen (17%), Infektionen (10%), Medikamente (6%), Hereditär (4%) und Idiopathisch (4%). Ein operativer Eingriff musste bei 20 Kindern (24%) durchgeführt werden. In 14 Fällen wurden die operativen Maßnahmen aufgrund der Gallenwegserkrankungen mit akuter oder chronischer Obstruktion des Ductus pancreaticus, durchgeführt. Die chirurgischen Eingriffe gliederten sich in: Cholezystektomie bei 8 Kindern, Hepatico-Jejunostomie bei 5 Kindern, Pancreatico-Jejunostomie bei 2 Kindern, Hepatico-Antrostomie bei 3 Kindern, Debridement und Drainage wegen

Pankreasnekrose im Rahmen der Chemotherapie aufgrund des Hodgkin-Lymphoms bei 1 Patienten, Resektion des Pankreasschwanzes nach Trauma bei 2 Patienten, und einer kombinierte Cholezystektomie und transduodenale Papillenplastik aufgrund einer sehr verengten Papilla Vateri in 1 Patient mit SPINK1 Mutation. Bei der Nachuntersuchung wurden 14 chirurgisch behandelte Patienten erfasst. Ein Todesfall aufgrund von assozierten Erkrankungen wurde registriert. Alle anderen Patienten haben keine wesentlichen Einschränkungen im Alltag!

Fazit: Pankreatitis im Kindesalter bleibt eine anspruchsvolle Erkrankung mit der Notwendigkeit einer chirurgischen Intervention, vor allem aufgrund der Obstruktion des Ductus pancreaticus, verursacht durch die zugrunde liegende Erkrankung der Gallenwege.

Abstract

Background: Pancreatitis is a rare disease in children which may be due to various causes requiring potentially specific treatments. The aim of this study was to evaluate the need for surgical therapy in children with pancreatitis.

Methods: Retrospective analysis of the complete clinical records of children aged 1 to 18 years who were treated for pancreatitis between 1991 and 2010 at the Department of Pediatric and Adolescent Surgery in Graz. Data were analysed regarding discharge diagnoses, age at presentation, length of hospitalization, gender, laboratory findings, imaging studies, etiology, therapy, and outcome. A follow-up study was performed at the median of 7 years and 11 months (1 to 20 years) after the surgery.

Results: Eighty-two children (46 boys, 36 girls), were treated during the study period. Mean age at presentation was 10.7±4.6 years. Sixty-seven children (82%) were treated for one episode of acute pancreatitis, 3 had acute recurrent pancreatitis and 12 children (15%) suffered from chronic pancreatitis. The most frequent imaging techniques used were: ultrasound (100%), computer tomography (43%) magnetic resonance imaging (23%), magnetic resonance cholangiopancreatography (23%) and endoscopic retrograde cholangiopancreatography (18%). Mean value of the maximum levels of serum lipase was 4531.4 U/l (-205), and of serum amylase 938.3 U/l (-100), respectively. Pancreatitis was found to be due to trauma (33%), biliary tract disorders (26%), secondary to other diseases (17%), infection (10%), drug induced (6%), hereditary (4%) and idiopathic (4%). Surgery was performed in 20 children (24%). In 14 cases surgery was due to biliary tract disorders with acute or chronic obstruction of the pancreatic duct. Surgery consisted of cholecystectomy alone in 8 children, hepaticojejunostomy in 5 children, pancreaticojejunostomy in 2 children, hepaticoantrostomy in 3 children, debridement and drainage due to pancreatic necrosis in the frame of chemotherapy for Hodgkin lymphoma in 1 patient, resection of the pancreatic tail due to trauma in 2 patients, and a combined cholecystectomy and a transduodenal papillosphincteroplasty due to a highly stenotic papilla Vateri in 1 patient with SPINK1 mutation. At the follow-up examination, 14 surgically treated patients were interviewed. One patient died due to the associated diseases. All other patients did not experience any substantial reduction of daily activities.

Conclusion: Pancreatitis in childhood remains a demanding disease. In one quarter of the patients there is a need for surgical intervention which is mainly due to pancreatic duct obstruction caused by the underlying biliary tract disorder.

Contents

Abbreviations

6-MP	6-Mercaptopurine
APACHE II	The Acute Physiology and Chronic Health Evaluation
ARDS	Acute Respiratory Distress Syndrome
BX	Biopsy
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CRP	C - Reactive Protein
CT	Computed Tomography
ERCP	Endoscopic Retrograde Cholangiopancreatography
EUS	Endoscopic Ultrasonography
I.V.	Intravenous
IBS	Irritable Bowel Syndrome
KUB	Abdominal x-ray
LFT	Liver Function Tests
MRCP	Magnetic Resonance Cholangiopancreatography
MRI	Magnetic Resonance Imaging
PRSS1	Cationic trypsinogen (UniGene name: protease, serine 1)
SIRS	Systemic Inflammatory Response Syndrome
SLE	Systemic Lupus Erythematosus
SPINK 1	Serine Protease Inhibitor Kazal Type 1 gene
TGF- β	Transforming Growth Factor
TNF-α	Tumor Necrosis Factor-α
US	Ultrasound

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1 Introduction -

1.1 Early concepts of pancreatic anatomy and physiology – a historical review

The early anatomical descriptions of the pancreas are considered to have originated from the Alexandrians Herophilus, Erasistratos and Eudemus in the third century BCE. Neither Hippocrates nor Erasistratus, or Herophilus could identify any connection of pancreas to any known diseases at their time [1]. Ruphos, an anatomist - surgeon of Ephesus, in the 1st or 2nd Century AD, named the organ "pancreas" (Greek pan: all, + kreas: flesh or meat). In Greek, the word meant "all flesh“ [1,2].

Galen (138-201 AD), taught that the role of pancreas was to protect the large blood vessels lying directly behind it. As the most famous physician of his time, Galen's word was "law" - and it was not confronted for well over a thousand years. Similar opinion shared also Andreas Vesalius (1513-1564) referring to the pancreas in the fifth book of his opus “De humani corporis fabrica” as a “glandulous organ growing in the nether panicle of the caule (omentum)” and claimed that the pancreas exercises a defensive effect on the stomach by serving as a pillow on which it rested [1].

Johan Wirsüng (1589-1643) described in year 1642 the main pancreatic duct, but neither he nor his contemporaries could interpret the function of the gland [1,2]. Giovanni Domenico Santorini (1681-1737) is credited with the discovery of the accessory pancreatic duct. In 1720, Abraham Vater (1684-1751) demonstrated his description of the duodenal ampulla, whereas Ruggero Oddi, as a fourth year-medical student in 1887, proved the existence of the sphincter, which bears his name [1].

Regardless of knowledge of pancreas existence, there was little attempt to explore the physiological function of the gland until the late 17th century when Franciscus de le Boe Sylvius (1614-1672) advised that digestion was a step-by-step process beginning with fermentation by saliva in the oral cavity and the abdomen. Then there is a second stage requiring the involvement of the pancreas, followed by the

extract of chyle into lymphatics, the venous system, and finally, the right side of the heart. His student Regnier de Graaf (1641-1673), ingeniously developed a method for the direct investigation of the nature of pancreatic juice by composing canine pancreatic fistulae through which he placed feather quills into the pancreatic ductal orifices to acquire succus pancreaticus. However, his examinations into the nature of the succus pancreaticus ended in his inaccurate conclusion that it was acidic in nature, because he had tested the pyloric antra of his piscine examples. These innovative theories on digestion were subsequently modified by John Conrad Brunner (1653-1727) whose experiments in pancreatectomized dogs led him to propose that specialized duodenal glands (which are named after him) were the major source of digestive juice secretion and that pancreas was not of vital importance neither for digestion nor for life [1].

In 1682, Peyer explained the lymphatic nodules found in the walls of the ileum and recommended that both Brunner glands and his own “patches” were support parts of digestion, manufacturing a fortifying secretion for the pancreatic juice. This reductionist perspective unfortunately slowed down pancreatic research for years based on the conclusion that pancreas was an insignificant contributor to digestion, whereas the stomach and the liver were raised as the key agents of digestion [1].

Willy Kuhne (1837 - 1900) and Alexander Marcet (1770 - 1822) provided additional explanation of pancreatic physiology such as identification of trypsin and its role in the digestion of protein, and discovery of lipase. Claude Bernard (1813-1878) of Paris demonstrated that gastric digestion “is only a preparation act” and that pancreatic extract emulsified fatty diets by partitioning them into glycerin and fatty acids. Furthermore, he demonstrated the part of the pancreas in the alternation of starch into sugar and its action on the “proteides that have not been cleaved in the stomach”. Eberle in 1843 described that pancreatic juice emulsified fat, and a year later, Valentin demonstrated its activity on starch. Ivan Pavlov (1849-1936) was one of the first who addressed the theory of the regulation of pancreatic secretion. Ivan Pavlov and his students mentioned a controlling part of the vagus nerve in the neural regulation of pancreatic secretion. In 1902, William Bayliss (1860-1924) and Ernest Starling (1866-1927) of University College, London, demonstrated that this phenomenon was also the effect of a chemical messenger and not only a neural

reflex. This led them to introduce the word “hormone” (derived from the Greek hormonos: I arouse to excitement) and name the putative agent “secretin”. Further progressions in this field included the discovery of cholecystokinin by A. C. Ivy (1893-1978) and E. Oldberg (1901-1986), and the understanding that a number of chemical messengers affected various aspects of pancreatic secretion (protein and water, bicarbonate) [1].

On the other side, D. Moyse, a student in Paris, in his thesis from 1852, may have been the first to describe the histology of the pancreas. In his thesis from 1869, Paul Langerhans ("Junior"), a student in the Berlin Institute of Pathology, which was directed by the eminent Professor Rudolph Virchow, described the islets of the pancreas, an endocrine system within the pancreas, which are today known as the "islets of Langerhans". His description was the first good histological description of the pancreas [2].

1.2 The pancreas – Anatomy and function

The pancreas lies parallel with and below the stomach. It is a transversely oriented retroperitoneal organ elongating from the "C" loop of the duodenum to the hilum of the spleen. Although the pancreas does not have well-defined anatomic parts, surrounding great vessels and ligaments can divide the organ into a head, neck, body, and tail [3]. The head sits to the right of L2; the body covers L1 and the tail rises to T12 on the left. The abdominal aorta and vena cava provide some absorbing effect against the vertebrae; however, particular forces (such as seat-belt and steering wheel injuries) can cause blunt trauma to the pancreas [4].

The splenic artery supplies the pancreas and lies along its superior border with the splenic vein. It seems that the blood supply is mostly concentrated into the head of the pancreas. The head of the pancreas shares its blood supply with the duodenum through the superior and inferior pancreaticoduodenal arteries [4].

The pancreas has vital endocrine functions, and the exocrine part of the pancreas is a crucial source of very potent digestive enzymes.

The endocrine part represents just 1% to 2% of the pancreas, and is composed of islets of Langerhans; these cells secrete insulin, glucagon, and somatostatin. The most serious disorders of the endocrine pancreas are diabetes mellitus and neoplasm [3].

The exocrine pancreas represents 80% to 85% of the pancreas, and is made of acinar cells that generate the digestive enzymes needed for digestion, and the ductules and ducts that transport them to the duodenum. The acinar cells produce most of the proenzyme forms of digestive enzymes (trypsinogen, chymotrypsinogen, procarboxypeptidase, proelastase, kallikreinogen, and prophospholipase A and B) and store them in membrane-bound zymogen granules. When acinar cells are triggered off to secrete, the granules merge with the apical plasma membrane and discharge their contents into the central acinar lumen. The most serious disorders of the exocrine pancreas include cystic fibrosis, congenital anomalies, acute and chronic pancreatitis, and neoplasms [3,5].

1.3 Organogenesis and exocrine histogenesis

The pancreas develops from two endodermal buds that originate from the caudal part of the foregut during the 4th week of gestation. One is the ventral bud, which arises from the bed of the hepatic diverticulum; the other originates from the dorsal surface of the duodenum. The ventral pancreatic bud rotates with the gut and merges with the larger dorsal primordium and with the duodenum. Then, the merged primordia takes up their regular place against the dorsal abdominal wall in the concavity of the duodenum. The ventral bud gives rise to the uncinate process and the inferior portion of the head of the pancreas. The dorsal primordium gives rise to the body, tail, and superior portion of the head. The duct of the dorsal pancreas opens further proximally into the duodenum and the ventral duct distally [4].

Fusion of the primordia during the 6th week of gestation leads to the fusion of the duct systems. The duct of the ventral pancreas becomes the main pancreatic duct of Wirsung. The duct of the dorsal pancreas usually remains patent as the minor duct of Santorini.

During the 7th week of gestation, undifferentiated epithelial tubules grow into a loose mesenchyme. The epithelium creates a duct system. Endocrine elements appear. From week 10 to term, the pancreas keeps on branching and gives rise to important exocrine and endocrine elements. Pancreatic exocrine maturation has been shown to be to a great extent a postnatal event. At birth, the acinar elements are underdeveloped, and increase rapidly after birth. Analysis of the morphologic maturement of an infant pancreas showed that the length of postnatal survival plays a far more important role than the gestational age [6].

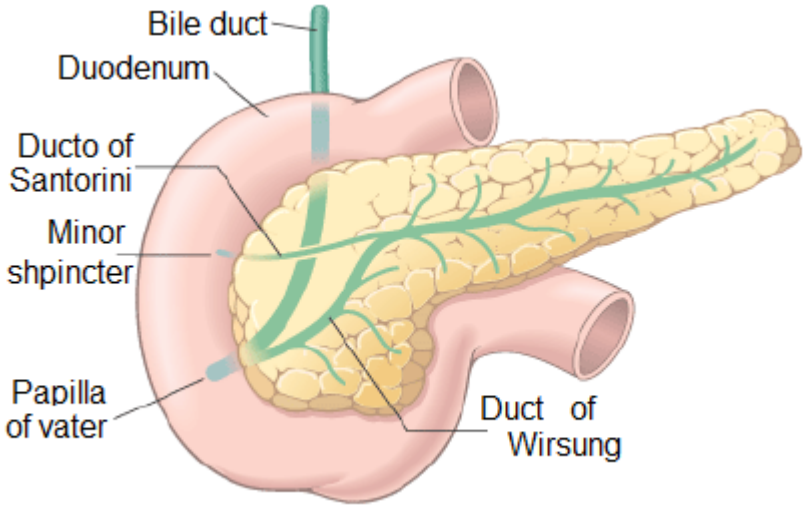

Figure 1: Pancreas, ducts, and derivation. The pancreatic duct of Wirsung drains most of the pancreas, joining the common bile duct proximal to the ampulla of Vater. The accessory duct of Santorini may drain part of the gland through a separate opening (With permission from: Gregg JA, Monaco AP, McDermott WV: Pancreas divisum: results of surgical intervention. Am J Surg 1983;145:488-492)

1.4 Congenital anomalies

As previously mentioned pancreatic development involves fusion of dorsal and ventral primordial. Slight changes in this progression often give rise to congenital deviations in pancreatic anatomy. While most of these deviations do not cause disease per se, variants, especially in ductal anatomy, can present unique obstacle to the endoscopist and surgeon. One of the examples is the failure to recognize distinctive anatomy, which could lead to unintended damage of a pancreatic duct during surgery [6].

1.4.1 Agenesis

Agenesis of the pancreas refers to a total lack of the gland, rather than a lack of the endocrine or exocrine parts alone [6]. This condition is very seldom, and usually not compatible with life. Insulin promoter factor-1 (IPF1) is a homeodomain transcription factor critical for normal pancreas development, and IPF1 gene mutations on chromosome 13q12.1 have been linked with pancreatic agenesis [3].

1.4.2 Pancreas divisum

Pancreas divisum is the most common congenital pancreatic anomaly. Pancreas divisum is often a cause of pancreatitis in children [7]. The fetal duct systems of the pancreatic primordia fail to merge, resulting in a very short main pancreatic duct (Wirsung) and draining only a small part of the head of the gland, while the bulk of the pancreas (from the dorsal pancreatic primordium) drains through the minor sphincter. The relative stenosis caused by the bulk of the pancreatic secretions draining through the minor sphincter, predisposes such individuals to chronic pancreatitis [3].

1.4.3 Annular pancreas

This anomaly happens in 1 to 20,000 births and it shows male predominance 2:1 [4]. Annular pancreas is a relatively unusual variant on pancreatic fusion; the consequence is a ring of pancreatic tissue that entirely circles the duodenum. From the first days of life, this anomaly causes symptoms of duodenal obstruction such as gastric distension and vomiting [3,4].

1.4.4 Ectopic pancreas

Ectopic pancreas occurs in about 2% of the population; preferred locations are the stomach and duodenum, followed by the jejunum, Meckel diverticulum, and ileum. These embryologic rests are relatively small (millimeters to centimeters in diameter) and are located in the submucosa; they are composed of normal pancreatic acini with occasional islets.

However, ectopic pancreas may cause pain deriving from localized inflammation up to mucosal bleeding, which occurs very rarely. Approximately, 2% of islet cell tumors originate for ectopic pancreatic tissue [3].

1.4.5 Congenital pancreatic cysts

Pancreatic cysts range from microscopic to 5 cm in diameter and very likely result from deviant ductal development. In polycystic disease, kidney, liver, and pancreas can all contain cysts. They may be covered by duct-type cube-shaped epithelium, or there might be a total absence of a cell lining, wrapped with just a

thin, fibrous capsule. Unilocular cysts tend to be benign, whereas multilocular cysts are more frequently malignant [3].

2 Pancreatitis

Pancreatitis is the inflammation of the pancreas associated with damage of the exocrine parenchyma of the pancreas. Severity of the clinical manifestations can range from a mild, self-limited to a life-threatening serious inflammatory process. The duration of the disease can range from a transient attack to a permanent loss of the function. Depending on the duration and recurrence, the inflammation may lead either to acute or to chronic pancreatitis. In acute pancreatitis, the gland can return to its normal function if the underlying cause of pancreatitis is removed. In direct comparison, chronic pancreatitis is defined by the permanent loss of exocrine pancreatic parenchyma [3].

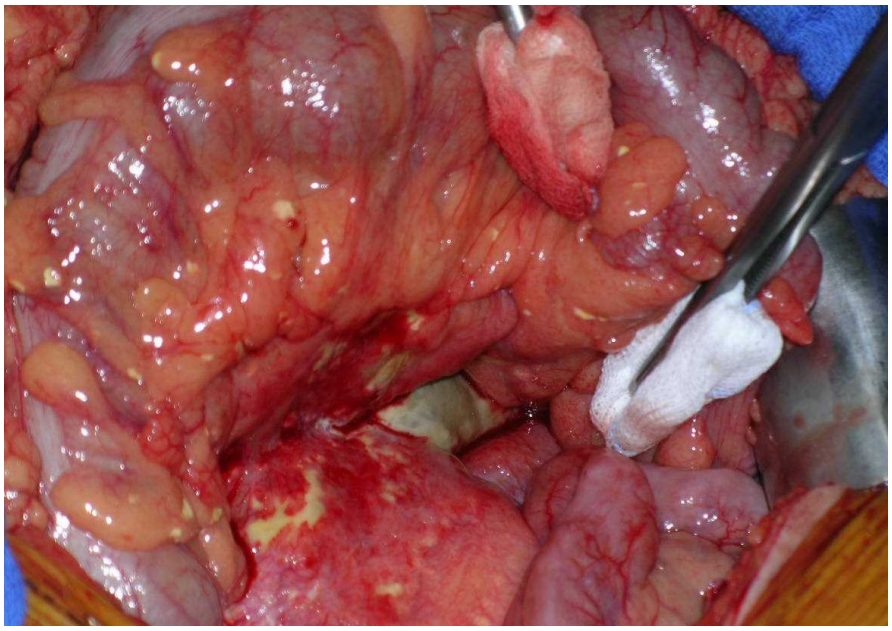

Figure 2: Necrotizing pancreatitis
(Courtesy of Medical University Graz)

Pancreatitis is rare during childhood and adolescence; nevertheless, it must be considered in every child with unexplained acute or repeated abdominal pain. The prognosis in children is usually good, except for pancreatitis occurring with multiorgan failure. Regardless of the underlying cause, specific common characteristics are found in all types of pancreatitis [4].

2.1 Acute pancreatitis

Acute pancreatitis is probably more common in childhood than it has been previously thought, and it may carry serious morbidity and mortality [8]. Nowadays, most pediatric centers treat five to ten acute cases of pancreatitis per year. The increase in the incidence of the disease from a previously reported figure of 1 in 500.000 children is a result of not only a better recognition, but also an increase in the number of infants and children directly exposed to blunt abdominal trauma and to the use of therapeutic drugs, which may cause pancreatitis [9].

2.1.1 Definitions and etiology

The definition of acute pancreatitis and its differentiation from chronic pancreatitis have been the topic of much debate. The definition accepted most widely holds that, the acute pancreatitis stands for a group of lesions mostly considered to be reversible like: edema, necrosis, hemorrhagic necrosis and fat necrosis, with the unexpected onset of the abdominal pain associated with a rise in acinar digestive enzymes in the blood or urine, lasting usually more than one day. Subsequently, an acute episode ends with the breakdown of symptoms, normalization of blood chemistry and complete restitution of pancreatic structure [4,10,11].

The most common cause for acute pancreatitis in adults is alcoholism followed by biliary tract disease usually due to obesity [9]. In children, however, the causes and clinical aspects of acute pancreatitis are different (Table 1), and the diagnostic criteria have been poorly defined. Most of the past reports consisted of limited case studies. A meta - analysis of 589 pediatric patients from 18 studies reported that etiology of pancreatitis in children as follows: idiopathic (23%), trauma (22%), structural anomalies (15%), multisystem disease (14%), drugs and toxins (12%), viral infections (10%), hereditary (2%), and metabolic disorders (2%) [8].

Abdominal trauma is most often caused by bicycle or sledding injuries, but also child abuse in young children. The poorly developed abdominal wall musculature and small anteroposterior diameter of the abdomen in children increase the danger of pancreatic injury in direct comparison to the adults. In children, direct trauma to the abdomen may cause contusion, laceration, or complete transection of the pancreas [9].

Pancreatic surgery and/or endoscopic retrograde cholangiopancreatography (ERCP) can also cause acute pancreatitis. The risk of developing acute pancreatitis after ERCP is estimated to be 5%. The essential risk factors for post-ERCP acute pancreatitis include female gender, presence of periampullary diverticulum, and procedure-related causes such as a cannulation time of more than 10 minutes and major papilla sphincterotomy [12].

There are also reported cases of acute pancreatitis in the postoperative period of various surgical procedures. The process that leads to acute pancreatitis during surgery, involves transient intraoperative hypotension or direct pancreatic trauma by intraoperative manipulation [12].

Various drugs may also cause acute pancreatitis. The use of L-asparaginase for leukemia therapy in oncology clinics caused an evident rise in acute pancreatitis in children [10]. The use of valproic acid, for the treatment of seizures, may cause both pancreatitis and hepatitis. Similarly, chlorothiazide and related thiazides have caused pancreatitis [9]. Use of organic acidemias and protease inhibitors in the treatment of acquired immunodeficiency syndrome (AIDS) have been recently defined as one of the causes for an acute pancreatitis [13].

Hypercalcemia and primary hyperparathyroidism count also as one of the causes leading to acute pancreatitis. Hypertriglyceridemia causes about 2% of acute pancreatitis, and is commonly associated with type I, Type II and Type V hyperlipidemia. Acute pancreatitis usually does not occur until serum triglyceride levels reach 1000 mg/dL. The triglyceride level should be measured as soon as clinical presentation of acute pancreatitis appears, considering that, this level tends to decline through hospitalization because of fasting and I.V. fluid resuscitation. Acquired hypertriglyceridemia can appear in children because of obesity and poorly controlled diabetes mellitus [12].

Pancreatitis appears only in 5% of patients with pancreas divisum, and it is thought to be the result of ductal hypertension caused by a narrow duct at its papillary origin [12].

Obstruction of the pancreatic ductal system by a tumor (pancreatic ductal carcinoma, ampullary carcinoma, islet cell tumor, solid pseudotumor of the

pancreas, sarcoma, lymphoma, cholangiocarcinoma, or metastatic tumor) can increase the intraductal pressure and lead to acute pancreatitis in proximately 14% of patients suffering from pancreatic tumors. This mechanism is also responsible for acute pancreatitis in 5% of patients with pancreas divisum [14].

In addition, a pancreatic cystic neoplasm, such as intraductal papillary-mucinous neoplasm, mucinous cystadenoma, or serous cystadenoma, can also cause acute pancreatitis [14].

Table 1: Etiology of acute pancreatitis in children

(With permission from: Nydegger A, Couper R, Oliver M. Childhood pancreatitis. J Gastroenterol Hepatol. 2006 Mar;21(3):499-509)

Acute Pancreatitis	
Drugs	Cimetidine Salicylates Paracetamol Cytotoxic drugs (i.e.L-asparaginase) Corticosteroids Immunosuppressive (particularly azathioprine and 6MP) Thiazides Sodium valproate Tetracycline (particularly if aged) Erythromycin Thiazides Valproic acid
Infections	Epstein–Barr virus Mumps Measles Cytomegalovirus Influenza A Mycoplasma Leptospirosis Malaria Rubella Ascariasis Cryptosporidium
Trauma	Blunt injury (handle bar, child abuse, etc.) Surgical trauma Endoscopic Retrograde Cholangiopancreatography
Metabolic	α-1 antitrypsin deficiency Hyperlipidemias Hypercalcemia
Toxin	Scorpion Gila monster Tropical marine snakes
Miscellaneous	Refeeding pancreatitis
Inflammatory/ Systemic disease	Hemolytic–uremic syndrome Reye's syndrome Kawasaki disease Inflammatory bowel disease Henoch–Schonlein purpura Systemic Lupus Erythematosus

2.1.2 Pathogenesis of acute pancreatitis

An inappropriate and early activation of trypsinogen to trypsin is a main pathogenetic mechanism leading to acute pancreatitis. Once activated these enzymes are responsible for autodigestion of pancreatic tissue resulting in necrosis of the acini and pancreatic islets with interstitial fat necrosis and necrotizing vasculitis [15].

Local inflammation leads to a release of active pancreatic enzymes into the bloodstream and stimulation of the production of inflammatory cytokines such as interleukin-1, interleukin-6 and interleukin-8 from neutrophils, macrophages and lymphocytes. The release of interleukins and tumor necrosis factor-α (TNF-α) from macrophages initiates an inflammatory cascade which leads to the systemic inflammatory response syndrome (SIRS). This systemic inflammatory response to pancreatic injury characterizes first 14 days of the disease and describes the “first or early phase” of the course of severe acute pancreatitis. In the early phase, organ failure is common and usually not associated with infection. The “second or late phase” which starts 14 days after the outbreak of the disease, is characterized by infection of the gland, necrosis and septic systemic complications causing an increase in mortality. Infection of the necrotic pancreas occurs in 8% to 12% of patients with acute pancreatitis and in 30% to 40% of patients with necrotizing pancreatitis, and is considered the most important risk factor of necrotic pancreatitis [12].

The mechanisms that trigger the activation of pancreatic enzymes are not entirely clear, but three possible events are discussed:

1. Pancreatic duct obstruction
2. Primary acinar cell injury
3. Defective intracellular transport of proenzymes within acinar cells [3].

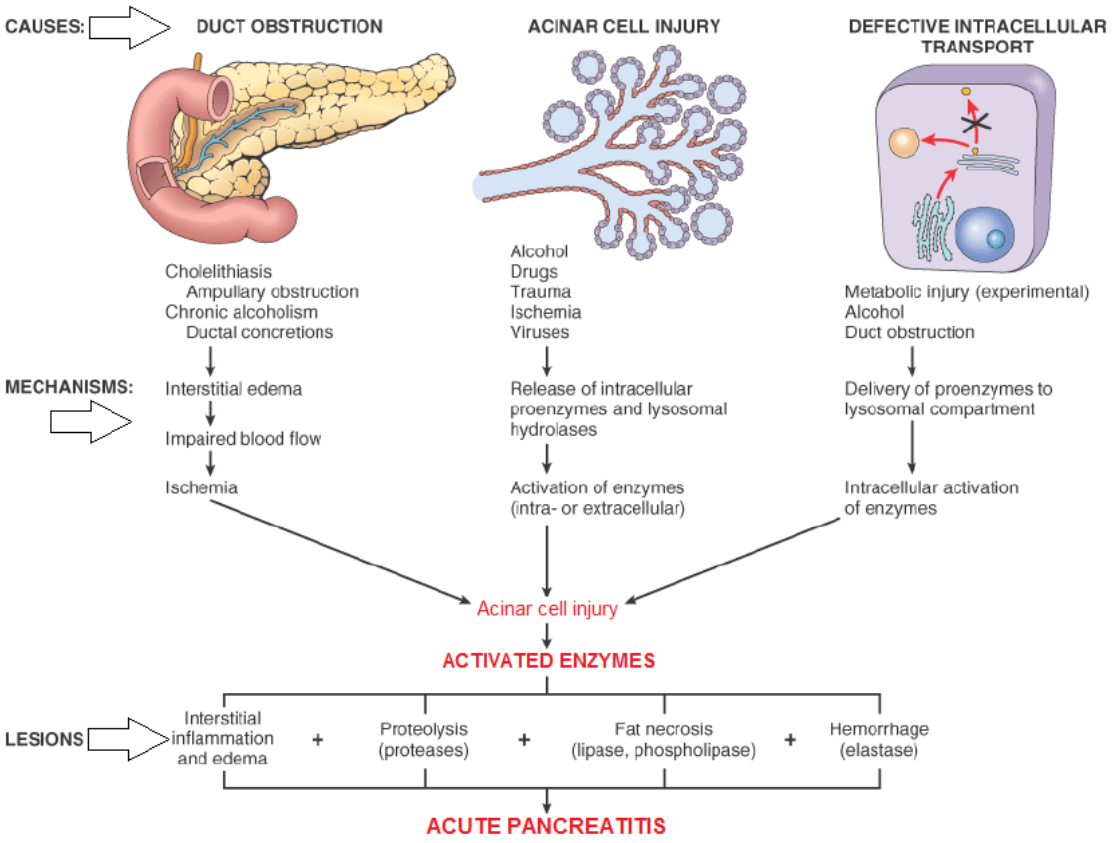

Figure 3: Three proposed pathways in the pathogenesis of acute pancreatitis. (With the permission from: Hruban R, Iacobuzio-Donahue Ch. The Pancreas. In: Schmitt W, Gruliow R, Sinclair J, Zanolle E, editors. Robbins' Basic Pathology. Philadelphia: Saunders Elsevier; 2010. p. 891-903)

2.1.3 Clinical manifestations and complications

Acute pancreatitis has a variable presentation in children. Symptoms may range from mild abdominal pain to severe systemic implication marked by metabolic disturbances and shock [10].

Children clinically often present with continuous, mid epigastric, and periumbilical abdominal pain. Vomiting, nausea and frequently fever are further common symptoms during the acute pancreatitis in children [13]. The pain can sometimes be both sudden in onset or slow and gradual. In spite of the fact that the most common location is the epigastrium, pain can be found in either the right or left upper quadrant. The characteristic radiation of the pain to the back seen in adults is not observed in most of children with acute pancreatitis [10].

The pain increases in severity for 24 to 48 hours. During this phase, vomiting may increase, and patients with such symptoms usually require hospitalization for fluid and electrolyte therapy [13].

Not always, there is a correlation between the physical findings and the severity of the disease. Tachycardia is usually present, and the abdomen is swollen and tender to palpation. Bowel sounds, disappear with the development of ileus. A rigid abdomen is unusual unless the pancreatitis is accompanied by a visceral perforation or severe intrapancreatic hemorrhage. In general, food aggravates pain and emesis. On careful diagnosis, the child may be ill, irritable, quiet, or all of these. Children typically lie still since movement exacerbates the pain, and on many occasions may get up on hand and knees in an effort to moderate pain [10]. Jaundice, ascites, and pleural effusions may occur in more severe cases [13].

A number of local and systemic complications may occur and are given in Table 2. Several scoring systems for acute pancreatitis are used in adults, but there is no entirely acceptable scoring system for reliably predicting disease severity in children [10,13].

Table 2: Complications of acute pancreatitis
(With permission from: Nydegger A, Couper R, Oliver M. Childhood pancreatitis. J Gastroenterol Hepatol. 2006 Mar;21(3):499-509)

Complication	
Local	Edema/inflammation Pancreatic necrosis Abscess Hemorrhage Fluid collections Pseudocyst Ductal rupture and stricture Extension to nearby organs
Systemic	Shock Pulmonary edema/effusions Hyperglycemia Hypocalcemia Multi-organ failure Renal failure Coagulopathy

2.1.4 Diagnosis

The diagnostic assessment of pancreatitis is linked to the accurate determination of the underlying etiology (Figure 4). Radiologic imaging of the pancreas is performed in addition to the clinical and biochemical assessment of pancreatitis and its complications [4,16].

Immediate diagnostic criteria are an elevated serum amylase and lipase. The serum amylase is normally less than 100 U/l and lipase less than 205 U/l. The serum amylase is elevated in 95 percent of patients with acute pancreatitis but may also be elevated in other conditions, such as: macroamylasemia, intestinal obstruction, renal insufficiency, mumps, ovarian pathology, acute appendicitis, parotid or salivary gland lesions, hepatitis and/or perforations of the small bowel [9]. Determination of amylase isoenzymes has also been used to increase diagnostic accuracy by specifying the tissue from which the amylase originates [4].

Serum amylase increases within 2–12 h after the onset of signs and symptoms of acute pancreatitis and, in simple cases, it remains elevated for 2–5 days. Serum amylase levels of greater than threefold normal levels are considered relevant for diagnosis. The sensitivity and specificity of amylase levels for pediatric acute pancreatitis are less accurate than in adults, which alter between 80% and 90% [10]. The urinary amylase level remains elevated at least one week after an acute pancreatitis episode and it can be used to document the disease after serum values have fallen. False positives have been reported in diabetic ketoacidosis, in fulminant alcoholic liver disease, and in burn patients; and false negatives can occur in renal failure. This analysis is not very reliable, and its value is now discussed controversially [9].

The level of serum lipase increases approximately 24 hours after onset of symptoms and remains elevated for longer than serum amylase levels. Furthermore, lipase has a greater sensitivity and specificity for acute pancreatitis than it has serum amylase. It is considered as highly consistent with pancreatitis when elevated greater than threefold the normal levels. The degree of elevation of other enzymes does not significantly match up with the severity of acute pancreatitis or its prognosis [9,10].

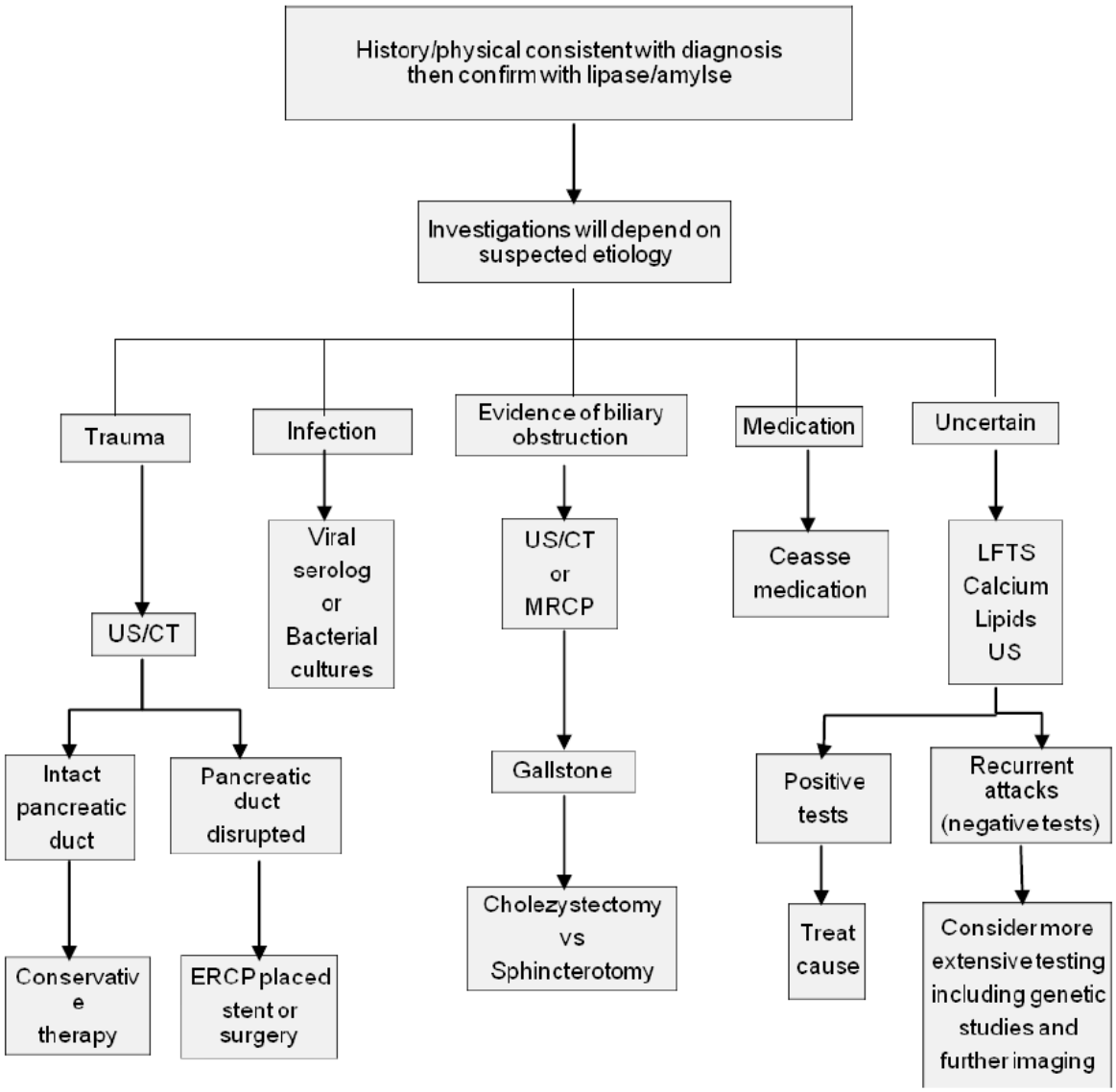

Figure 4: Diagnostic algorithm for acute pancreatitis

(With permission from: Nydegger A, Couper R, Oliver M. Childhood pancreatitis. J Gastroenterol Hepatol. 2006 Mar;21(3):499-509)

Modern imaging techniques help confirm the diagnosis of pancreatitis, and may often successfully identify the cause of it, and reveal potential complications such as pseudocysts. Among the most useful and frequently used imaging techniques are abdominal ultrasound and computed tomography (CT) [10].

Ultrasound is usually the first imaging examination modality in a patient with an acute abdomen. However, associated paralytic ileus can limit ultrasound diagnosis of acute pancreatitis during the first 48 h [17]. The two major sonographic findings are enlarged pancreas and reduced pancreatic echogenicity. A normal gland can be observed in mild cases [10,17]. The published sensitivity for diagnosing acute pancreatitis by ultrasound (US) is around 62–67% [10].

CT is the most useful imaging method used to evaluate patients with acute and chronic pancreatitis, but radiation exposure with this method is high. CT is indicated when:

1. There is a history of significant blunt abdominal trauma or if one is concerned about other serious intra-abdominal disorders such as mesenteric infarction as a cause of severe pain;

2. Severe pancreatitis needs to be staged (particularly to look for evidence of necrosis, which is often not noted for 48–72 h after the disease onset), and

3. There is a suspicion for significant intraabdominal complications of pancreatitis [10].

Spiral CT allows scanning of the complete pancreas during a single breath hold. CT scan can provide early conclusion about the disease, indicate the severity of illness, disclose associated complications, and ensure efficacy of percutaneous therapy. 20% of patients with acute pancreatitis will have a normal CT examination [4,13].

ERCP is seldom required for acute pancreatitis; however, it ultimately turns out to be necessary in any child who has pancreatitis with an unclear cause. This procedure is useful in cases of relapsing pancreatitis related with pancreaticobiliary malunion [4,16]. ERCP is, still an invasive method that can exacerbate the pancreatitis and is not preferred during the acute stage of pancreatitis [4].

Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive approach of acquiring images of the pancreaticobiliary tract. MRCP visualizes the common bile duct in more than 96% of patients and exposes common bile duct stones with a sensitivity of 71% to 100%, thus clearly exceeding the sensitivity of US (20% to 65%) and CT (45% to 85%). Visualization of the smaller pancreatic duct is successful in more than 80% of patients [4], even though experience in children is limited [10].

Radiographic examinations enhanced by water-soluble contrast of the upper gastrointestinal tract are sometimes useful, especially in cases of trauma when the injury to the duodenum or small intestine is suspected [4].

2.1.5 Treatment

The therapy of acute pancreatitis is based upon a considerable knowledge of the pathophysiology involved. Primary goals are:

1. maintenance of adequate circulating intravascular volume,
2. minimization of pancreatic endocrine and exocrine activity, and
3. prevention or treatment of complications associated with acute pancreatitis.

This includes also appropriate use of analgesics, maintenance of nutrition, and prevention of infection [4,9,10,13,16].

At the beginning, the patient is fastened and nasogastric suction used to decrease vomiting and distension and to reduce the secretin release secondary to duodenal acidification [9]. Most mild to moderate pancreatitis will recover soon if food and drinks are deliberately withheld for 3–5 days. During this time, it is essential to maintain hydration by administration of i.v. fluids, and control pain with parenteral analgesia. It is traditional to give meperidine rather than morphine because the latter causes ampullary spasm [4,10,13].

Oral feeding must be withheld in order to reduce pancreatic stimulation; however, enteral nutrition should be initiated as soon as possible to avoid malnutrition. The results of several controlled studies in adult patients with acute pancreatitis support early enteral nutrition [18,19,20]. According to these studies, tube feeding considerably reduced mortality, multiple organ failure, systemic infections, and the need for operative interventions compared to those who received parenteral nutrition. In addition, there was a tendency towards a reduction in a length of hospital stay. These data recommend that enteral nutrition should be considered as the standard care for patients with acute pancreatitis [18,20].

Although there are relatively few pediatric data on this subject, enteral nutrition has been widely accepted. A naso-jejunal feeding tube is placed either radiologically or

endoscopically, and the child is fed with high-protein and low-fat nutrition until he or she is ready to commence oral intake [10].

The hematocrit, hemoglobin, white blood cell count, serum calcium, glucose, and electrolytes should be measured, and urine output observed hourly [4,9]. Extremely aggressive volume resuscitation carries the risk of fluid overloads. Fluid overload bears the risk of inducing pulmonary edema [21].

A recently completed prospective cohort study with 247 patients came to conclusion that the administration of a small amount of fluid during the initial 24 h was not associated with a poor outcome and the patients did not have an increased incidence of necrosis. During this study patients were divided into three groups according to the amount of fluid administered during the first 24h. First group received less than 3.1 l; second group between 3.1 l and 4.1 l; and the third group more than 4.1 l of fluid. Patients who received between 3.1 l and 4.1 l of fluid during the first 24h had an excellent outcome. Patients who received less than 3.1 l of fluid did not have a poor outcome. The need for a great amount of fluid (> 4.1 l) during the first 24h was associated with a poor outcome; the administration of a great amount of fluid during the initial 24 h was associated with organ failure and local complications [22].

Current medical care of acute pancreatitis is primarily supportive with the main goal to control the disorder before the need for surgical intervention becomes necessary, which is rarely required complications such as a pseudocyst or an abscess [4,9].

In cases of a pseudocyst, which is the most common complication of traumatic pancreatitis, the operative intervention should be attempted only after the cyst matures. In cases with abscess formation, antibiotic therapy with external surgical drainage is required [9,16].

In general, patients with acute pancreatitis due to underlying pancreaticobiliary disease require surgical correction of the underlying condition before cure can be expected.

In the management of severe acute pancreatitis, a major decision to be made is whether and when surgery for pancreatic necrosis or infection is required. Infection

of necrotic pancreatic tissue is a significant risk factor for mortality in severe acute pancreatitis and is an indication for surgery. On the other hand, nonsurgical care of sterile pancreatic necrosis, including antibiotic treatment is strongly supported. Fine-needle aspiration to detect infection in necrotizing pancreatitis is studied in adults and children and it has been shown that patients may be referred to surgery only if infection is confirmed [4,16,23]. Surgical procedure is considered the gold standard treatment for proven infected pancreatic necrosis [12]. The published death rate is 1.8% with sterile pancreatic necrosis and 24% with infected necrosis. Early surgery has been associated with increased mortality and should be postponed, if it cannot be avoided [4,16,23].

Pancreatitis as the consequence of trauma may involve anatomic fractures of the gland, parenchyma, and/or duct transection. In such cases, debridement and drainage are inadequate and subtotal pancreatectomy with distal drainage is usually required [9].

2.2 Chronic pancreatitis

2.2.1 Definitions and etiology

Chronic pancreatitis is described as inflammation of the pancreas with gradually progressive and irreversible destruction of pancreatic parenchyma, including pancreatic exocrine acinar cells, ductule structures, and in the late stages, the destruction of endocrine islet cells. This destruction, by either necrosis or scarring and atrophy, induces eventually pancreatic exocrine and endocrine insufficiency [3,10,11,16,24].

Usually, symptoms commence in the first decade of life but normally are mild at onset. Spontaneous recovery from each attack happens in 4 to 7 days, but episodes become gradually more severe, and after a few years, exocrine and endocrine insufficiency develops, and acute attacks decrease and disappear [11,13].

The most common causes of chronic pancreatitis in children are systemic disease, malformations of the pancreaticobiliary tree and heredity (Table 3). In addition, various unusual conditions, including metabolic disease, endocrine disorders, and inflammatory bowel disease, may cause the disease [4,10,16].

There are certain circumstances in which the destruction of the pancreas begins antenatally. Infants with Shwachman-Diamond Syndrome, an autosomal recessive disorder with pancreatic insufficiency at birth present mostly with very low serum trypsinogen levels indicating nearly entire exocrine pancreatic atrophy at birth [9,13,16,25].

Furthermore, the latest developments in molecular biology and in our understanding of inflammation (discovery of mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), cationic trypsinogen gene (PRSS1), pancreatic secretory trypsin inhibitor (also known as SPINK 1) and the action of cytokines), have advanced our understanding into the pancreatic process resulting in chronic pancreatitis [10].

Table 3: Etiology of chronic pancreatitis in children

(With permission from: Nydegger A, Couper R, Oliver M. Childhood pancreatitis. J Gastroenterol Hepatol. 2006 Mar;21(3):499-509)

Chronic Pancreatitis	
Chronic Pancreatitis in childhood	Cystic fibrosis Fibrosing pancreatitis Hereditary chronic pancreatitis Juvenile tropical pancreatitis Inborn errors of metabolism Idiopathic chronic pancreatitis Trauma
Congenital anomalies of the pancreatic duct	Pancreaticobiliary malunion Pancreas divisum Annular pancreas
Biliary tract disorders	Choledocholithiasis Cholelithiasis
Chronic inflammatory conditions	Crohn's disease Ulcerative colitis Systemic lupus erythematosus
Chronic hereditary pancreatitis (diagnosed mainly in adult life)	Hyperlipidemias Partial lipodystorphie Wilson's disease Hemochromatosis α-1 antitrypsin deficiency

Several studies reported an increased frequency of CFTR gene mutations in patients with pancreatitis, particularly in patients with idiopathic-juvenile chronic pancreatitis. This condition leads to cystic fibrosis - the most common inherited disorder of the exocrine pancreas, which is characterized by respiratory disease and pancreatic dysfunction [26].

In cystic fibrosis (CF), almost all infants have a certain degree of chronic pancreatic inflammation, manifested in significantly elevated serum trypsinogen, a characteristic that is particularly assigned as a sensitive neonatal screen for cystic fibrosis. Approximately, 85% of these infants will progress to complete atrophy. Loss of more than 97% of pancreatic function is required, for clinical observation of pancreatic insufficiency with fat malabsorption and steatorrhea [3,10,13,16].

Genetic defects in the cationic trypsinogen gene (PRSS1) result in pancreatic autodigestion due to either increased activation or prevented inactivation of pancreatic enzymes within the acinus [10,27,28].

The function of serine protease inhibitor SPINK1 is the effective protection of the pancreas from autodigestion by inhibiting prematurely activated trypsinogen. SPINK1 hinders trypsin directly at the active catalytic site. The SPINK1 mutation is noticeably increased among the patients with idiopathic chronic pancreatitis (approximately 25%) [10,29].

2.2.2 Pathogenesis of chronic pancreatitis

Nearly all individuals with recurrent episodes of acute pancreatitis develop chronic pancreatitis. It has been suggested that acute pancreatitis triggers a sequence of perilobular fibrosis, duct distortion, and changed pancreatic secretions. Over time and with numerous episodes, this can lead to loss of pancreatic parenchyma and fibrosis [3].

Types of chemokines have been identified in chronic pancreatitis, including IL-8 and monocyte chemoattractant protein. In addition, the macrophages, suppress acute inflammation by releasing TGF- β and other cytokines, which stimulate pancreatic stellate cells to produce and deposit collagen, and eventually resulting in pancreatic fibrosis, a distinctive characteristic of chronic pancreatitis. While the chemokines produced during chronic pancreatitis are similar to those produced in acute pancreatitis, the profibrogenic chemokines tend to predominate in chronic pancreatitis [3,30].

2.2.3 Clinical manifestations and complications

Chronic pancreatitis may present in many different forms, but there are 3 major clinical features consisting in pain, maldigestion and diabetes.

Abdominal pain leads to considerable morbidity in chronic pancreatitis. It is most frequently described as deep or penetrating epigastric pain, and may radiate to the back and also be accompanied by nausea and vomiting. It is often relieved by sitting forward and may increase post-prandially. Although frequent or persistent pain is considered to be the hallmark of chronic pancreatitis, a subgroup of

patients may have no pain at all, because over time, there is a trend for the pain to decline or totally “burn out”, presenting instead with symptoms of pancreatic insufficiency. Severe pain decreases appetite, thereby contributing to malnutrition and weight loss [3,10,31].

Steatorrhea as a further important characteristic of chronic pancreatitis is a symptom of advanced disease and does not occur until pancreatic lipase secretion is lowered to less than 10% of the normal output. Maldigestion of lipids occurs earlier than that of other nutrients since lipase secretion declines more rapidly than protease or amylase secretion [10,31].

Apart from exocrine insufficiency, in chronic pancreatitis in the long-term also diabetes mellitus develops. This is basically due to a destruction of the islets of Langerhans, respectively destruction of both - insulin and glucagon producing cells [3,10,31].

The complications of chronic pancreatitis are summarized in Table 4.

Table 4: Complications of chronic pancreatitis
(With permission from: Nydegger A, Couper R, Oliver M. Childhood pancreatitis. J Gastroenterol Hepatol. 2006 Mar;21(3):499-509)

Complication	
Pancreatic pseudocyst	Pseudoaneurysm
Splenic vein thrombosis	Common bile duct obstruction
Duodenal obstruction	Pancreatic fistula
Adenocarcinoma	

2.2.4 Diagnosis

The diagnosis of the disease is based on a combination of clinical features (abdominal pain, weight loss and diabetes mellitus), functional (documented exocrine pancreatic insufficiency) and imaging studies. In adult patients, pancreatic biopsy is considered the gold standard for diagnosis, but this is seldom if ever performed in children [10,31].

The extent of permanent damage to the pancreas may be carefully evaluated by blood tests (pancreatic enzymes), stool tests (pancreatic enzymes, fecal fat), and noninvasive tests of pancreatic function, such as the pancreatic stimulation (secretin) test [4]. Clearly, the diagnosis of severe chronic pancreatitis with widespread calcifications and ductal dilatation is simple. The difficulty in diagnosis begins in patients with early, mild, or minimal pancreas changes, characteristic pancreatic pain alone, patients in whom chronic pancreatitis is being distinguished from pancreatic malignancy, and in patients with a late episode of acute pancreatitis [27].

The indirect tests, although less expensive, detect abnormalities secondary to loss of pancreatic function such as malabsorption of fat and nitrogen. However, these tests lack both sensitivity (less than 60%) and specificity, and cannot adequately distinguish between mild and moderate exocrine pancreatic function. That is why none of them per se are especially helpful in diagnosing chronic pancreatitis [10,31].

Except indirect test, there are also direct tests (Table 5), which are highly sensitive and specific, but invasive and time-consuming tests of exocrine function, which include small intestinal intubation tests to estimate the secretory capacity of the pancreas [10].

Table 5: Tests of exocrine pancreatic function
(With permission from: Nydegger A, Couper R, Oliver M. Childhood pancreatitis. J Gastroenterol Hepatol. 2006 Mar;21(3):499-509)

Direct tests
Exogenoous hormonal stimulants (secretin and CCK)
Nutrient stimulants (Lundh test meal, fatty acids, amino acids and hydrochloric acid)
Indirect tests
Stool (microscopy for fat globules, 72-h fecal fat balance, chymotrypsin and elastase)
Breath tests (carbon-14-lipids, carbon-13-lipids and starch)
Urinary and plasma markers (bentiromide, pancreolaryl, dual-label Schilling)

Imaging procedures used in children and adults with chronic pancreatitis include US (less frequently endoscopic ultrasonography), CT, endoscopic retrograde cholangiopancreatography (ERCP), MRCP and MRI [4,10,17,27,32].

US is ideal for examining the pancreas in children. Smaller size of patients and lack of fat make US of the pancreas more applicable than in adults [32].

Findings consistent with chronic pancreatitis include:

- dilation of the pancreatic duct;
- ductal stones;
- irregularities in gland margins and changes in echotexture; and
- pseudocysts [4,10,31].

Ultrasound is said to have a sensitivity of 50–80% and a specificity of 90%. Endoscopic ultrasound displays a highly detailed study of the pancreatic duct and parenchyma [10].

CT is effective for visualizing the size of the pancreas and its ducts and for detecting small calculi that may be overlooked on plain radiographs and US. However, in patients with early chronic pancreatitis, the role of CT is limited, because of the technical limitations of CT, which makes it difficult to identify the earliest changes in chronic pancreatitis [4,27].

ERCP is an important tool in the diagnosis as well as in the management of chronic relapsing pancreatitis in children and adults. ERCP is demanding and a difficult procedure to perform in infants and toddlers. The complication rate of ERCP documented in the studies ranges from 0–11% [32]. The most common indications for ERCP in children are biliary obstruction and pancreatitis. It's accuracy in diagnosing ductal abnormality is up to 90% [4,32]. The sensitivity and specificity approaches 90–100% [10,27].

In the era of MRCP, the role of ERCP has become more of an interventional tool. MRCP has the main advantage of being non-invasive, without radiation exposure [4,10,27,32]. MRCP visualizes the ducts in their normal physiologic state, whereas

at ERCP, they are imaged under pressure. MRCP can adequately provide a thorough morphology of the biliary and pancreatic ducts [32]. It is possible to depict ducts as small as 1 mm. MRCP is highly sensitive and specific for pancreas divisum. However, it is difficult to visualize pancreatic ducts and abnormalities such as pancreas divisum and anomalous union of the pancreaticobiliary junction in children less than two years of age [33].

In addition, here is worth mentioning the role of secretin, a polypeptide hormone, which induces increased fluid signal in pancreatic duct and subsequent fluid excretion into the duodenum. Secretin is probably more important in children than in adults as it increases the detectability of the normally smaller pancreatic ducts. The role of secretin respectively visualization on MRCP before and after secretin administration has been presented by Darge et al. [32] and Chahvan et al. [33]. According to their data in children with idiopathic chronic pancreatitis who were submitted to MRCP before and after secretin administration, the number of pancreatic ducts visualized on MRCP, improved after administration of secretin. The peculiarity of cavities and main pancreatic duct outline irregularity improved too [32,33].

Benefit of MRCP in children is restricted by the need for sedation or anesthesia, high cost, limited availability, and long scanning times [33]. Except MRCP, MRI and US are progressively becoming valuable radiation-free modalities of choice for the diagnosis of acute and chronic pancreatitis in children [32].

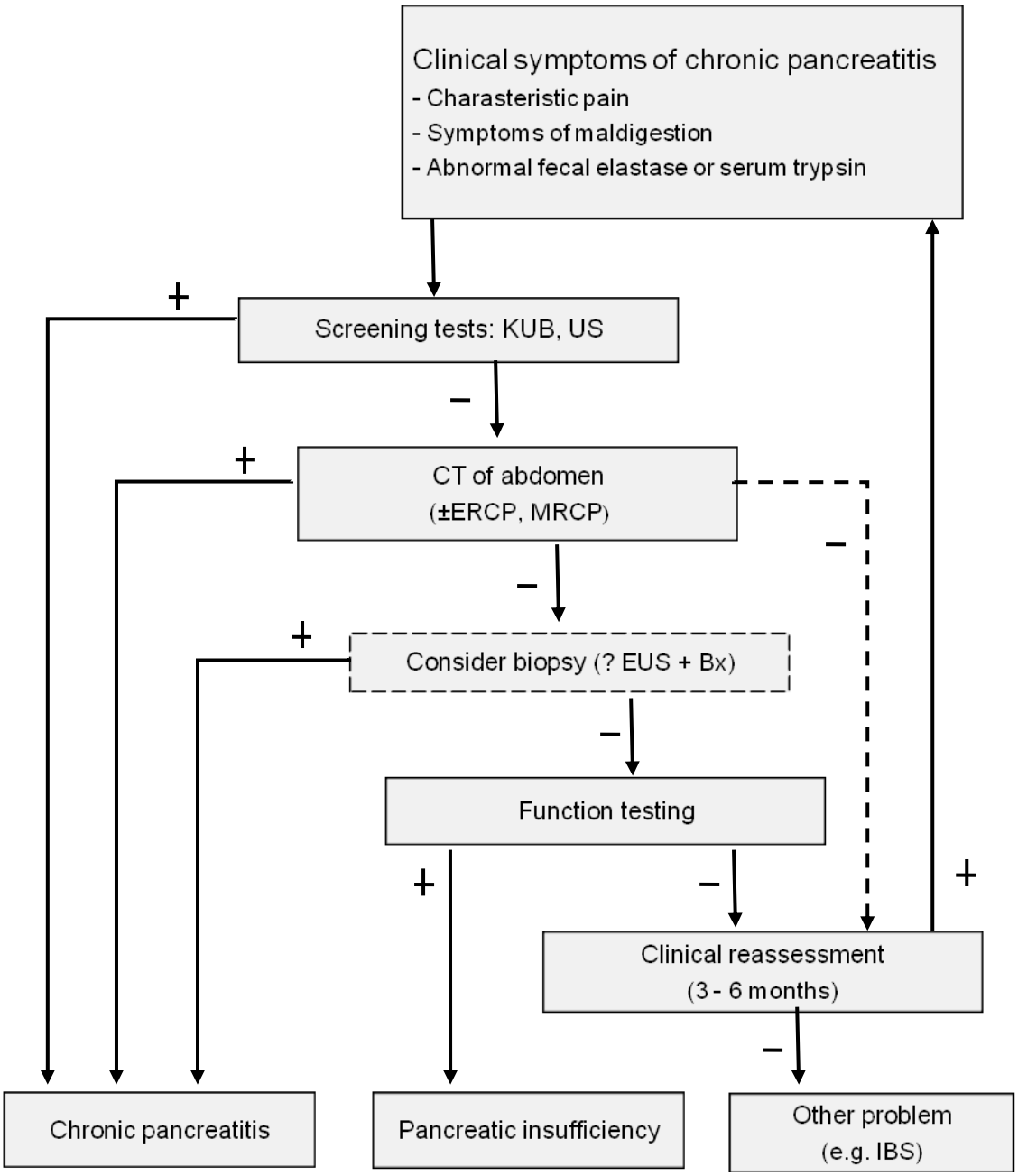

Figure 5: Algorithm for the evaluation of suspected chronic pancreatitis (With permission from Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology 2001; 120:682-707)

2.2.5 Treatment

The treatment of chronic pancreatitis is principally symptomatic and is directed toward the essential hallmarks of pain, and exocrine and endocrine insufficiency. However, if a relevant cause such as an anatomic anomaly or a metabolic disease can be identified, it may be managed by surgical or medical intervention [31].

In general, the therapeutic schemes for chronic pancreatitis should be directed towards:

- etiological investigations;
- adequate analgesia;
- providing proper long-term follow up with attention on monitoring and treatment of exocrine pancreatic insufficiency and diabetes mellitus; and
- providing patient education with particular attention to avoidance of smoking and alcohol (both risk factors for the development of pancreatic adenocarcinoma) [10].

Regardless of the cause, chronic pancreatitis in children has a continual progression that has been especially difficult to treat medically [34], and this is the main indication for endoscopic therapy and surgery. The prime goal of these interventions is the arrangement of adequate drainage of the pancreatic ducts. Again, pediatric data are infrequent and limited to small case studies, and a decision concerning surgery in children is often based on adult experience. Endoscopic therapy refers to stent placement and is helpful only if there is a visible dominant stricture with evidence of pancreatic duct obstruction [10].

Indications for surgery include also complications such as common bile duct or duodenal obstruction, and/or failure of endoscopic therapy in a patient with complex pain [31].

Surgery on the pancreas is generally of three types:

1. sphincteroplasty;
2. pancreatic drainage via longitudinal pancreaticojejunostomy (Puestow) or end-to-end pancreaticojejunostomy (DuVal); and
3. pancreatogastrostomy (Smith) and pancreatectomy [4].

Surgical interventions have been shown to have a good short-term and long-term remission of pain and are related to minimal morbidity and mortality. It is also known that earlier operative intervention correlates with better long-term protection of pancreatic function [35].

Although somewhat controversial, aggressive operative therapy for chronic pancreatitis in the adult has been shown to be effective in preserving pancreatic function in many adult patients who fail non-operative treatment, but its wide application in children has been limited [34].

3 Methods

This retrospective study was conducted at the Department of Pediatric and Adolescent Surgery of the Medical University of Graz. The charts of all patients in whom one of the discharge diagnoses was pancreatitis and who were treated in the period between August 15, 1991 to August 15, 2010 were reviewed. Data were collected from the patient management program “MEDOCS”, and were evaluated in Microsoft Office Excel 2007.

Criteria for the diagnosis of pancreatitis were the threefold elevation of serum lipase above the upper reference level.

The medical charts of all patients under the age of 18 years were identified and reviewed for age at presentation, gender, length of hospitalization, peak serum amylase and lipase levels, etiology, clinical and laboratory findings, imaging studies performed, type of treatment, outcome and mortality.

After the full hospital record review, telephone consultations using the standardized questionnaire were used to determine the long-term follow-up. In case of complaints the patients were examined in the outpatient office.

3.1 Ethics

Ethical approval for the study was obtained from the Research Ethics Committee of the Medical University of Graz, Austria (EK-Number: 23-425 ex 10/11) before commencement of the project.

3.2 Statistical analysis

All data were analyzed using Microsoft Office Excel 2007. The charts and tables were also created with Microsoft Office Excel 2007.

4 Results

4.1 Patients

Eighty-two patients (46 male and 36 female) were treated during the study period between 1991 and 2010. After the year 1996 (*n* = 8), a continuous decrease in the number of patients admitted for pancreatitis was observed (Fig. 6).

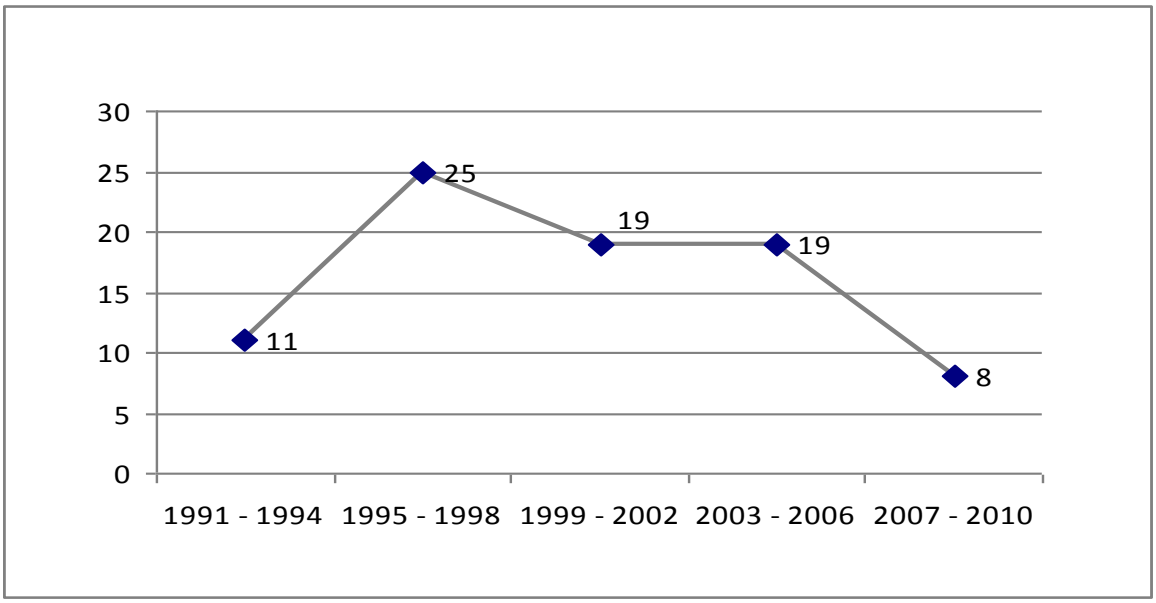

Figure 6: Distribution of patients admitted for treatment due to pancreatitis, pooled into four-year periods from 1991 to 2010.

The relationship between the age of patients and number of patients per each age during the study period is shown in Figure 7.

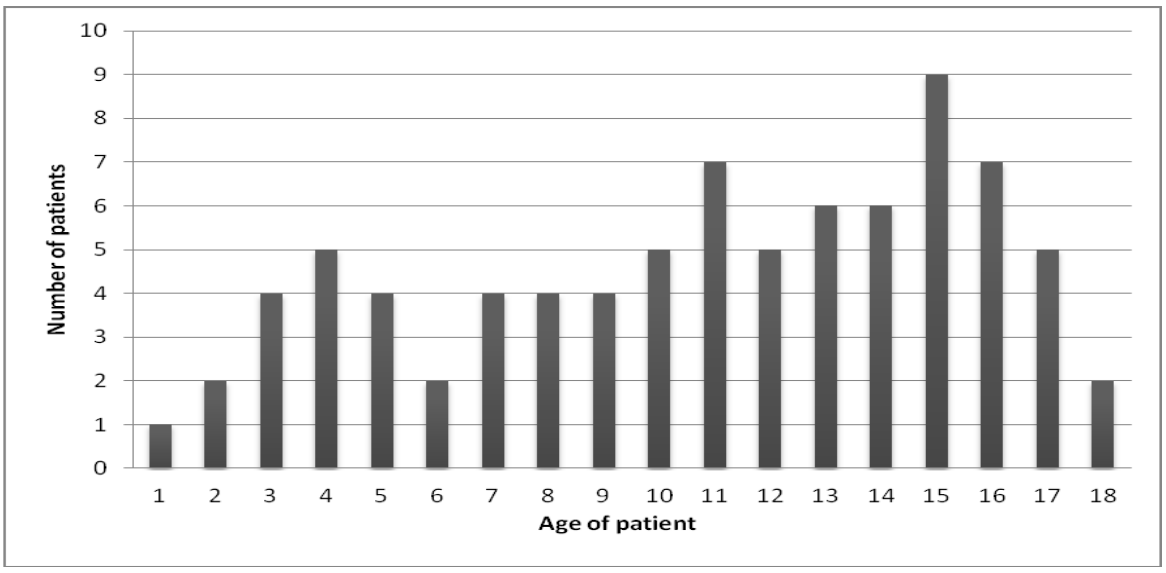

Figure 7: Allocation of the patient's number according to patient's age during the study period.

The majority of patients were older than 10 years of age.

Figure 8 shows the distribution of gender and age in our patients with pancreatitis. Interestingly, in the age group of 1 – 6 years there were twice as much female patients (12:6), whereas in the age groups of > 6 years the opposite was the case (24:40).

Also, whereas the number of female patients did not change with increasing age, the number of male patients increased with age; from 6 patients in the youngest group (1 – 6 yrs) to 23 patients in the oldest group (13 – 18 yrs).

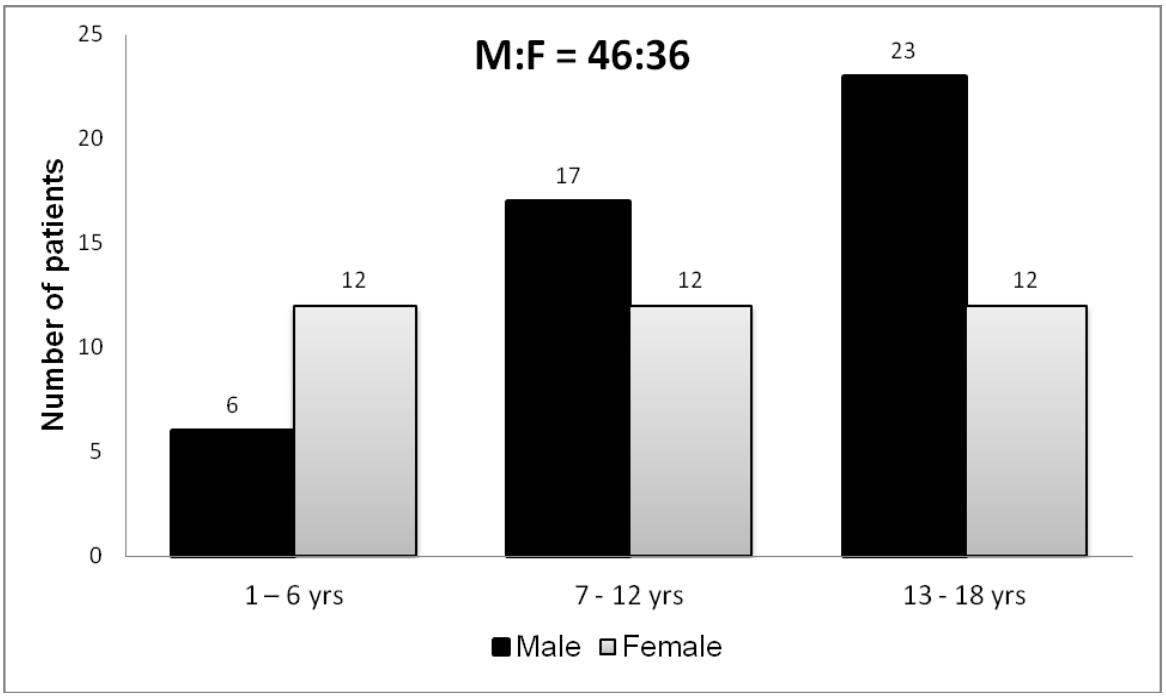

Figure 8: Gender and age distribution of 82 pediatric patients with pancreatitis

4.2 Length of hospitalization

The median duration of hospitalization was 14 days (range 3 – 104 days). The majority of our patients remained in the hospital for less than 20 days during the first episode of pancreatitis (*n* = 53; i.e. 65%).

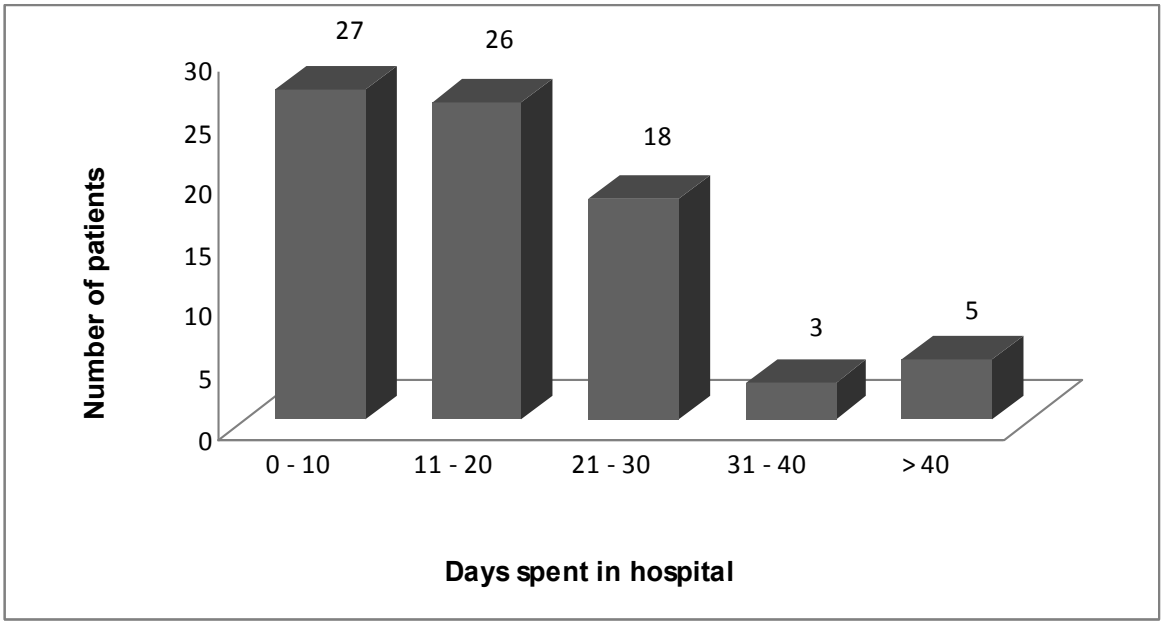

Figure 9: Duration of hospitalization during the first episode of pancreatitis

Data concerning the length of hospitalization during the first episode of pancreatitis were missing in three patients.

These patients suffered from:

1. Chronic pancreatitis due to SPINK-1 mutation
2. Acute pancreatitis secondary to the subphrenic abscess
3. Acute relapsing pancreatitis due to choledochal cyst.

4.3 Laboratory findings

The peak increase in amylase and lipase levels was analyzed.

The mean value of serum lipase was 4531.4 U/l (normal < – 205 U/l), Std. Error = 722.1, range from 301 to 31.794 U/l; and serum amylase 938.3 U/l (normal < – 100 U/l), Std. Error = 171.9, range from 212 to 938.3 U/l.

Ten patients have not reached the >3 time elevation of lipase value, however they had an elevated lipase serum level from 301 till 605 U/l, where the normal value is – 205 U/l.

Two of them were suffering from chronic pancreatitis due to a common channel and choledochal cyst. In the setting of long-standing disease, 3-fold elevations of lipase serum level were not present because of fibrotic changes in the pancreas. Four patients suffered from injuries (spleen rupture, heavy headache) due to trauma. In 2 patients with elevated lipase serum value (406 U/l and 529 U/l, respectively) Epstein-Barr-Virus was found with otherwise unclear cause of acute pancreatitis. One patient had an elevated lipase serum value (595 U/l) after an appendicovesicostomy surgery and one patient (555 U/l) after a perforated appendicitis.

Except the patient who underwent a surgery, the rest referred to hospital because of epigastric or abdominal pain. In 2 patients, pain was accompanied by vomiting.

4.4 Imaging of pancreas

Imaging studies were regularly performed. Abdominal ultrasound examination was used as the primary imaging modality to assess the morphology of pancreas in all our patients.

Computer tomography scans were performed in 35 patients, MRI as well as MRCP in 19 patients (23%), and ERCP in 15 patients (18%) were performed.

Thirty patients (37%) had just one imaging modality (US); 52 patients (63%) had more than one imaging modality; the most common combination was US and CT, performed in 35 patients (43%).

CT and MRI together, were performed in 11 patients (13%).

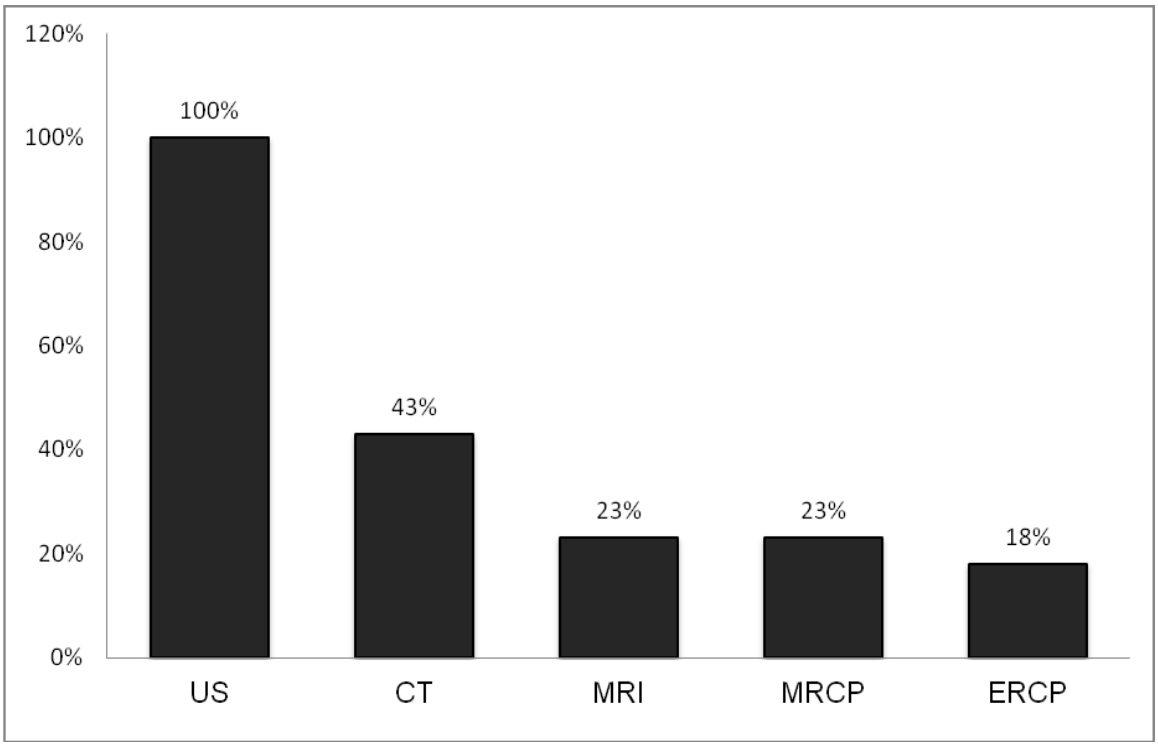

Figure 10: Imaging techniques used in patients with pancreatitis

4.5 Etiology

Figure 11 shows that trauma and biliary tract disorders are the most common cause of pancreatitis in children in the present study.

A number of our patients had a complex disease course, experienced multiple medications and had operative procedures for various underlying conditions. Therefore, it was not always easy to specify the accurate etiology of pancreatitis.

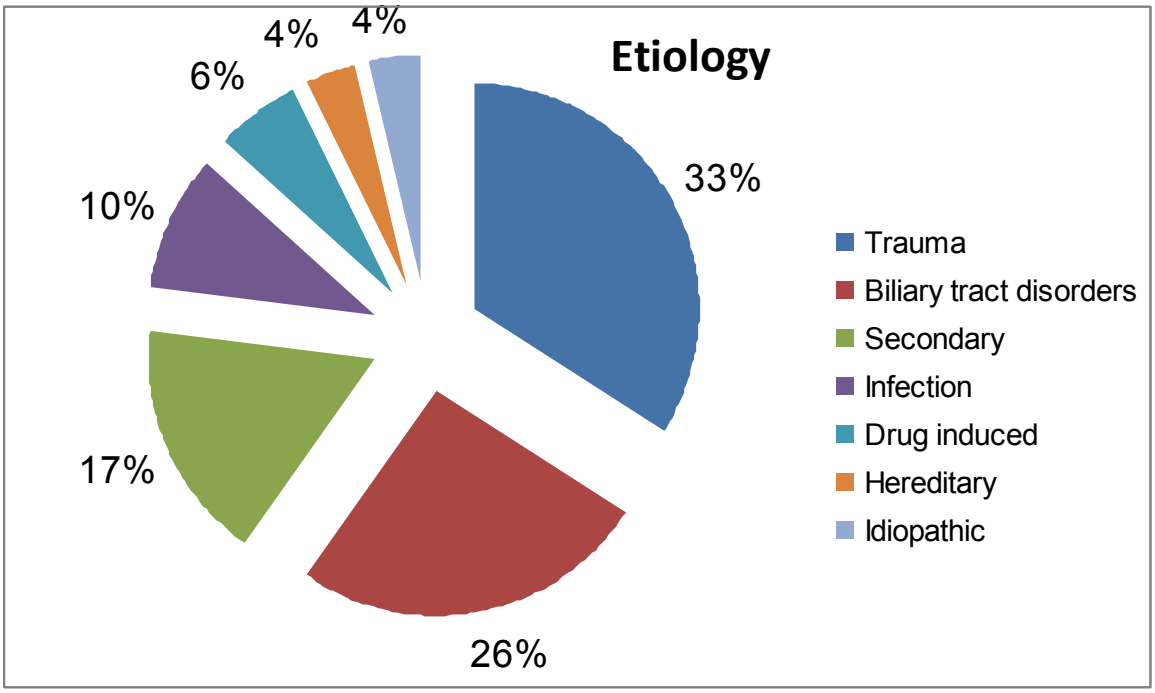

Figure 11: Etiology of pancreatitis in our patients (*n* = 82)

To assess the etiology of pancreatitis various tests were performed when needed. The easiest group for assessment of etiology was the abdominal trauma group, followed by the group of biliary tract disorders due to gallstones (*n* = 10). In 3 patients mutations in genes leading to pancreatitis were found, whereas in other 3 patients despite of various examinations no etiologic cause of pancreatitis could be found and these patients were classified as idiopathic pancreatitis cases.

Fourteen patients had other severe diseases leading to surgical intervention and developed pancreatitis in the frame of their primary disease. These cases were diagnosed as secondary pancreatitis.

In 8 cases infections with various agents possibly leading to pancreatitis were found and these patients were classified in the group of pancreatitis due to infection.

Five patients developed pancreatitis due to drug therapy of their primary disease (neoplasia and epilepsy). These patients were classified under drug induced pancreatitis (Table 6).

Ten patients with anatomic abnormalities of the biliary tree and one patient with microcholelithiasis required multiple imaging and diagnostic modalities and were classified under biliary tract disorder.

Table 6: Etiology of pancreatitis in our 82 patients

Trauma (*n* = 28)

- Blunt trauma (*n* = 27)
- Penetrating trauma (*n* = 1)

Biliary tract disorders (*n* = 21)

- Cholecystolithiasis (*n* = 10)
- Common channel (*n* = 6)
- Choledochal cyst (*n* = 4)
- Microcholelithiasis (*n* = 1)

Secondary (*n* = 14)

- Organ perforation (*n* = 7)
  - Perforated Appendicitis (*n* = 5)
  - Perforated Choledochal cyst (*n* = 1)
  - Subphrenic abscess (*n* = 1)
- OP and Post-Op (*n* = 6)
- Ileum intussusception and infarction (*n* = 1)

Infection (*n* = 8)

- Viral (*n* = 4)
  - Epstein-Barr virus (*n* = 3)
  - Rotavirus (*n* = 1)
- Bacterial (*n* = 4)
  - Campylobacter jejuni (*n* = 2)
  - Staphylococcus aureus (*n* = 1)
  - Haemophilus influenza (*n* = 1)

Drug induced (*n* = 5)

- Neoplasia (*n* = 4)
- Valproic acid (*n* = 1)

Hereditary (*n* = 3)

- SPINK 1 – Mutaion (*n* = 3)

Idiopathic (*n* = 3)

4.5.1 Etiology in correlation with age and gender

Table 7 shows the age and gender distribution of our patients according to the etiology of pancreatitis. Of note is the similar distribution of biliary tract disorders over different age groups, however, in the younger patients the biliary tract disorders were due to anatomic anomalies of the biliary tree whereas in the older patients' biliary tract disorders were due to gallstone disease.

Also, of note is the high number of patients with trauma and secondary pancreatitis in the age group of 13 – 18 years (*n* = 21).

Table 7: Age, gender and etiology

	A g e					
	1 – 6 years		7 – 12 years		13 – 18 years	
Etiology	Male (*n* = 6)	Female (*n* = 12)	Male (*n* = 17)	Female (*n* = 12)	Male (*n* = 23)	Female (*n* = 12)
Trauma	2	3	8	3	10	2
Biliary tract disorder	1	4	4	5	2	5
Secondary	1	3	0	1	7	2
Infection	2	1	2	2	0	1
Drug induced	0	0	0	0	4	1
Hereditary	0	1	2	0	0	0
Idiopathic	0	0	1	1	0	1

4.5.2 Etiology and hospitalization

Table 8, shows the correlation between the days spent in hospital and the etiology of pancreatic disease. Forty-one percent of patients with biliary tract disorders were hospitalized for less than 10 days. These are patients with gallbladder stones. In a group of patients hospitalized for > 40 days, 60% of them suffered from trauma with multiple bone fractures and head injuries.

Table 8: Duration of hospitalization in relation to the etiology of pancreatitis

Etiology	Hospitalization in days					
	0 – 10 (*n* = 27)	11 – 20 (*n* = 26)	21 – 30 (*n* = 18)	31 – 40 (*n* = 3)	> 40 (*n* = 5)	Missing data (*n* = 3)
Trauma	5	10	9	1	3	0
Biliary tract disorder	11	5	2	0	2	1
Secondary	1	6	5	1	0	1
Infection	2	4	1	1	0	0
Drug induced	3	1	1	0	0	0
Hereditary	2	0	0	0	0	1
Idiopathic	3	0	0	0	0	0

4.5.3 Etiology and imaging

In 37% of the cases, the information from US was sufficient to determine the cause of pancreatitis. This number include 11 patients with pancreatitis secondary to other disease, 9 patients with trauma, and also 5 patients with gallstones. US as the only imaging modality was performed also in 3 patients with infection as the cause of pancreatitis, in one patient with drug induced pancreatitis and in one case with idiopathic cause of pancreatitis (Table 9).

Twenty patients (57%) with acute pancreatitis due to trauma had a CT scan, beside US. CT was also performed in 6 patients with biliary tract disorders, with the main suspicion of choledochal cyst.

Five patients (53%) with pancreatitis due to biliary tract disorders had an MRI. Four patients with pancreatitis induced by drugs had also an MRI. Three of them were suffering from T-Cell Non Hodgkin Lymphoma and one from epilepsy. MRI was also performed in 3 patients with acute pancreatitis due to trauma.

Fifty-three percent of total MRCP imaging sessions were performed in 10 patients with pancreatitis due to biliary tract disorders. Three patients with SPINK-1 mutation had MRCP too.

ERCP was mainly performed in patients with biliary tract disorders (67%). Six of 10 patients with biliary tract disorders, receiving ERCP had confirmed common channel. Two other patients suffered from cholecystolithiasis and other two from choledochal cyst.

Table 9: Etiology and imaging modalities

		Imaging modality				
		US	CT	MRI	MRCP	ERCP
E	Trauma	28	20	3	1	0
t	Biliary tract disorder	21	6	5	10	10
i	Secondary	14	2	3	1	1
o	Infection	8	3	1	2	1
l	Drug induced	5	3	4	1	0
o	Hereditary	3	1	2	3	1
g	Idiopathic	3	0	1	1	2
y	Total	82	35	19	19	15

4.6 Type of pancreatitis

The vast majority of 82 children, had just one episode of acute pancreatitis (*n* = 67), whereas 15 patients suffered from more than one episode of pancreatitis (Table 10).

A cause for acute pancreatitis was found in 66 (98%) patients. These include trauma (*n* = 28), secondary to other diseases (*n* = 14), biliary tract disorders (*n* = 12) and infection (*n* = 8).

In one case no cause of acute pancreatitis could be found and this case was classified as idiopathic acute pancreatitis.

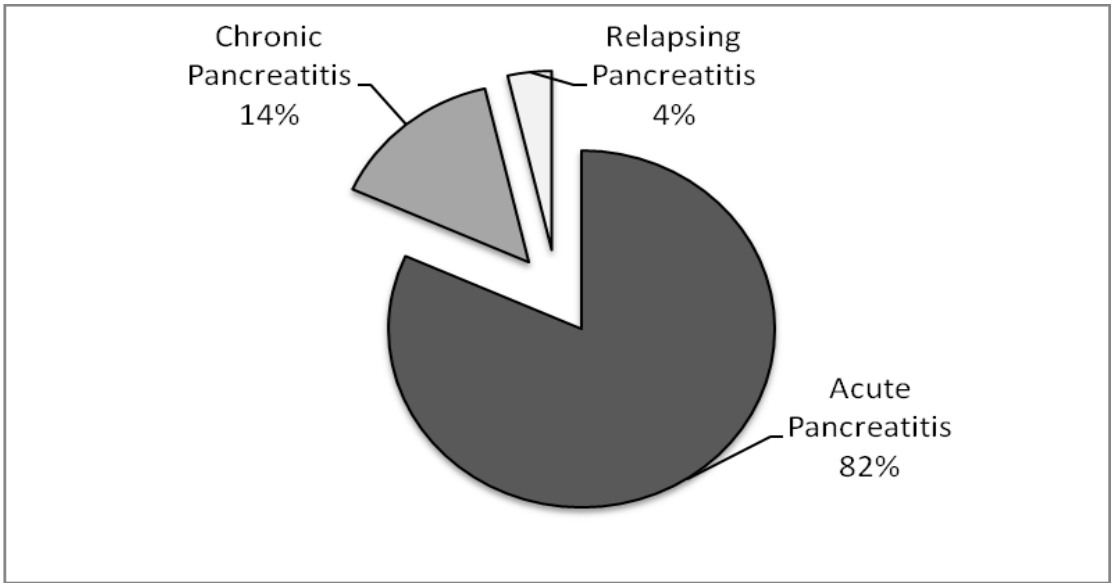

Figure 12: Types of pancreatitis in 82 patients. Data are presented in %

Causes for chronic pancreatitis were biliary tract disorders (*n* = 7), SPINK-1 mutation (*n* = 2), drug induced - due to chemotherapy for T-cell Non-Hodgkin lymphoma (*n* = 1) and in two cases no cause of chronic pancreatitis could be found, and these were classified as idiopathic cases of chronic pancreatitis.

Figure 13 shows the gender and age distribution among our patients with acute pancreatitis. Of note is the relatively high difference between the number of male and female patients with acute pancreatitis, in the age group of 13 – 18 years (22 : 9).

In age group of 1 – 6 years and in the group 7 – 12 years there is no such a big difference between the number of male and female patients with acute pancreatitis.

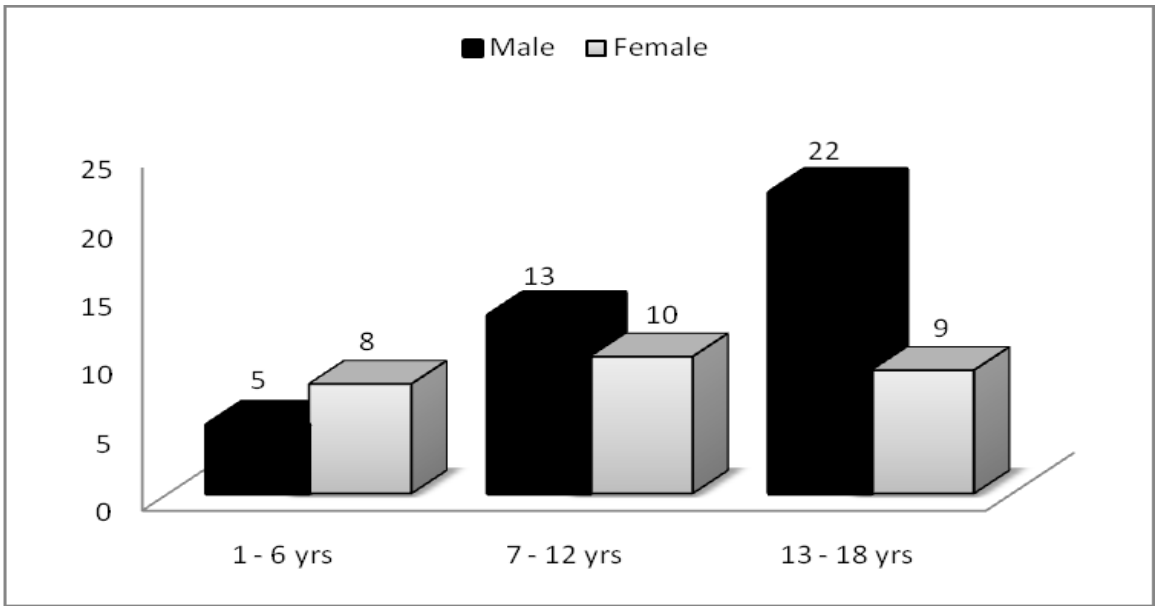

Figure 13: Gender and age distribution of 67 pediatric patients with acute pancreatitis

Whereas in the age group of 13 -18 years acute pancreatitis is more often in boys, in the group of 1 – 6 years female patients with chronic pancreatitis are more common (80%). Also in the group of 13 – 18 years of age there is a ratio of 2:1 in favor of male patients.

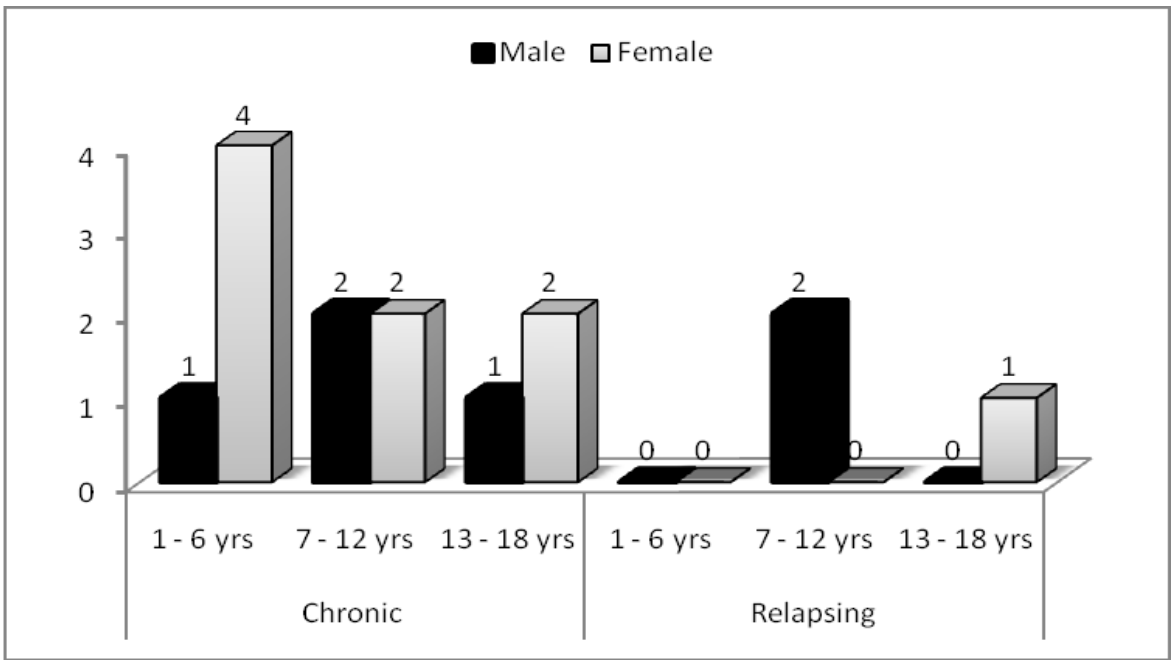

Figure 14: Gender and age distribution of 14 pediatric patients with chronic and relapsing pancreatitis

Table 10 shows that all of our trauma patients (*n* = 28), were treated for solely one episode of acute pancreatitis, which makes almost half (42%) of all patients with acute pancreatitis (*n* = 67). Second most common cause of acute pancreatitis was secondary to other diseases 21%.

On the other hand, the most common causes for chronic and acute relapsing pancreatitis were biliary tract disorders with 58% (7 out of 12 patients), and 66% (2 out of 3) of all cases (Table 10), respectively.

Table 10: Diagnosis in correlation to etiology

	Diagnose		
Etiology	Acute Pancreatitis (*n* = 67)	Chronic Pancreatitis (*n* = 12)	Relapsing Pancreatitis (*n* = 3)
Trauma	28 (42%)	0 (0%)	0 (0%)
Biliary tract disorder	12 (18%)	7 (58%)	2 (66%)
Secondary	14 (21%)	0 (0%)	0 (0%)
Infection	8 (18%)	0 (0%)	0 (0%)
Drug induced	4 (9%)	1 (8%)	0 (0%)
Hereditary	0 (0%)	2 (17%)	1 (34%)
Idiopathic	1 (2%)	2 (17%)	0 (0%)

4.7 Treatment

Most of our patients could be managed non-operatively; however in 20 patients (24%) a surgical intervention was needed (Fig. 15).

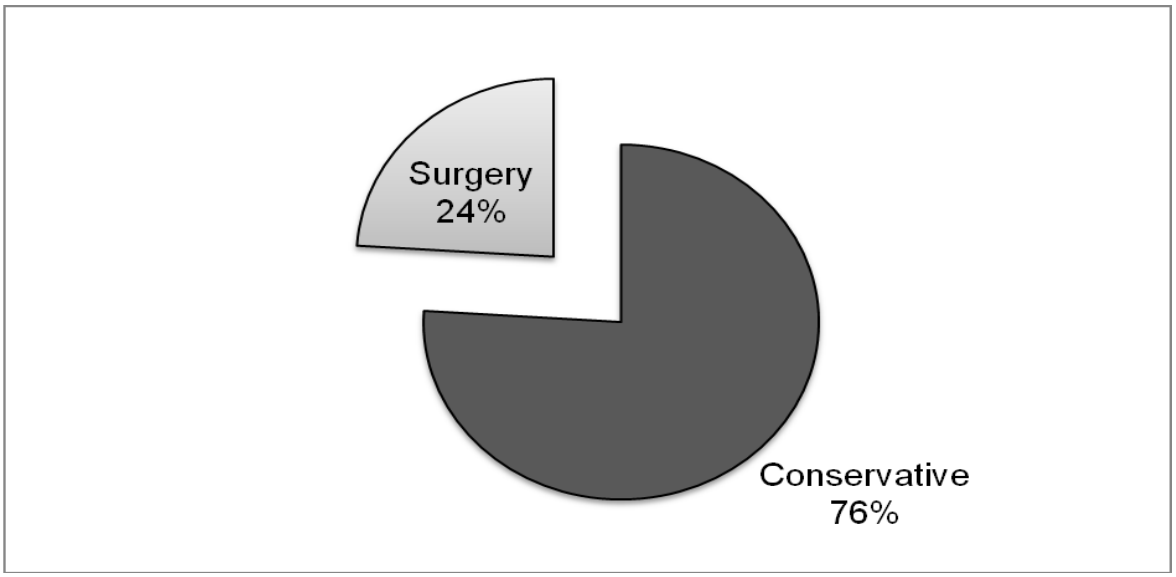

Figure 15: Proportion between operative and non-operative therapy of our patients with pancreatitis

4.7.1 Non-operative treatment

Sixty-two patients received non-operative treatment (38 male and 24 female). Twenty-six of them (41%) suffered from trauma, 13 patients (21%) suffered from pancreatitis secondary to other diseases, 8 (13%) suffered from systemic infection, 7 (11%) had pancreatitis due to biliary tract disorders, 4 patients (6%) suffered from drug induced pancreatitis, 3 patients (5%) suffered from idiopathic pancreatitis and 1 patient had pancreatitis due to a SPINK-1 mutation (Fig. 16).

The majority of these patients (n = 56; 90%) had just one episode of acute pancreatitis. The main cause for acute pancreatitis among these 56 patients was: trauma (*n* = 26), secondary to other disease (*n* = 13), systemic infection (*n* = 8), biliary tract disorder (*n* = 5), drug induced acute pancreatitis (*n* = 3) and idiopathic (*n* = 1). Gallstones (*n* = 4) and choledochal cyst (*n* = 1) were causes for acute pancreatitis in 5 patients with biliary tract disorder.

Four cases with chronic pancreatitis were treated non-operatively. Two of them had chronic pancreatitis due to unknown causes, one had chronic pancreatitis due

to a choledochal cyst and one patient suffered from drug induced chronic pancreatitis.

In addition, one patient with microcholelithiasis and one patient with SPINK-1 mutation received non-operative treatment because of acute relapsing pancreatitis.

Duration of hospitalization in patients who received a non-operative treatment was between 3 and 57 days (median 14 days).

Chronic pancreatitis patients who received non-operative treatment spend 10 to 44 days (median 17.5 days) in the hospital.

All children who had a non-operative treatment were evaluated by ultrasonography of the pancreas and biliary tree (*n* = 62). Additionally, where needed CT (*n* = 26), MRI (*n* = 12) and MRCP (*n* = 12) and ERCP (*n* = 4), were performed.

From 24 patients non-operatively treated who received a CT scan, 18 (75%) CTs were performed due to trauma. Six other patients received a CT-scan due to systemic infection (*n* = 3), secondary to other disease (*n* = 1), drug induced acute pancreatitis (*n* = 1) and choledochal cyst (*n* = 1).

Further, 2 patients had a CT examination for evaluation of their chronic pancreatitis, which was in 1 case drug induced and in the other due to choledochal cyst, respectively.

MRI and MRCP were performed in 7 non-operatively treated patients with acute pancreatitis due to gallstones (*n* = 1), choledochal cyst (*n* = 1), systemic infection (*n* = 1), blunt trauma (*n* = 1), secondary to other diseases (*n* = 1), drug induced (*n* = 1) and idiopathic (*n* = 1) causes.

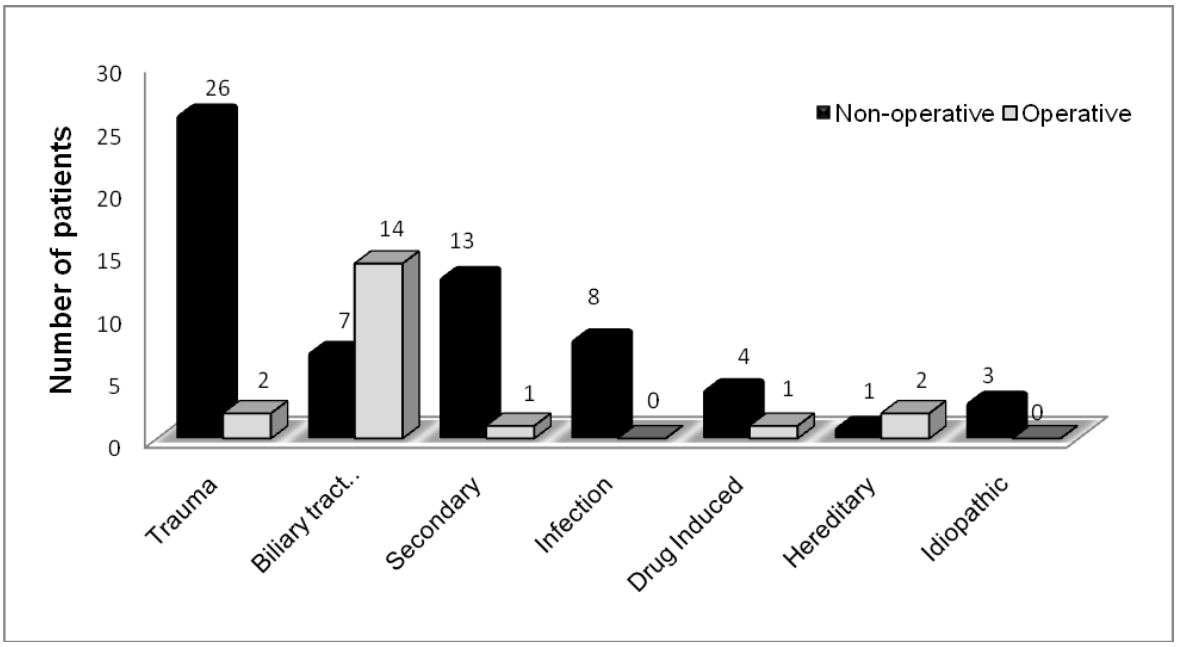

Figure 16: Type of treatment in relation to etiology of pancreatitis

4.7.2 Operative treatment

Out of 20 patients, who underwent a surgical procedure 12 were female and 8 were male. Eleven patients were suffering from acute pancreatitis (55%), one patient from acute relapsing pancreatitis and 8 patients received surgery due to chronic pancreatitis.

Clearly, the most common etiological factors leading to the need for surgical intervention were biliary tract disorders, which constitute 70% of all operative cases, followed by hereditary (*n* = 2), trauma (*n* = 2), drug induced (*n* = 1) and secondary to other disease (*n* = 1) (Fig. 16).

Acute pancreatitis in operatively treated patients was caused by gallstones (*n* = 6), common channel (*n* = 1), trauma (*n* = 2), secondary to other diseases (*n* = 1) and drugs (*n* = 1). Eight patients with chronic pancreatitis, who underwent surgery had their pancreatitis caused by: common channel (*n* = 5), choledochal cyst (*n* = 1) and SPINK-1 mutation (*n* = 2).

All children who underwent surgery were evaluated by ultrasonography of the pancreas and biliary tree (*n* = 20). Additionally ERCP (*n* = 11), CT (*n* = 9), MRI (*n* = 7) and MRCP (*n* = 7) were performed.

In 3 cases the information got from a US was conclusive and there was no need for further imaging modalities. These were simple cases with pancreatitis due to gallstones in adolescents.

ERCP was performed in 7 patients with chronic pancreatitis. The main reason for using ERCP was the investigation of the pancreatic and biliary tree. In 5 cases a common channel was found, in one case a choledochal cyst and in one case multiple stenosis of the pancreatic duct.

In addition, ERCP was performed in 4 patients with acute pancreatitis and operative treatment. Patients had biliary tract disorder with gallstones (*n* = 2), common channel (*n* = 1); and perforated cholecystitis *(n* = 1), respectively.

CT scans were performed in 5 operatively treated patients with acute pancreatitis due to trauma (*n* = 2), then common channel, perforated cholecystitis and drug induced (*n* = 1).

Four patients with chronic pancreatitis who underwent a surgical procedure, 2 patients with common channel, one patient with choledochal cyst, and one patient with SPINK-1 mutation received also a CT scan.

MRI and MRCP were performed in 3 patients with chronic pancreatitis who underwent a surgical procedure due to SPINK-1 mutation (*n* = 2) and common channel (*n* = 1).

Hospitalization of patients who received an operative treatment because of acute pancreatitis was between 4 and 104 days (median 8.5 days). Patients with chronic pancreatitis who received an operative treatment spend 9 to 27 days (median 22 days) in hospital.

The patients were discharged 3 to 54 days postoperatively (median, 10 days). During the postoperative stay in a hospital, all patients received antibiotics and analgesics; and they all were on pancreas diet. Also, majority of patients received proton pump inhibitors (Losec®), and only 5 patients received digestive enzyme (Creon®).

Fourteen (70%) of the 20 surgically treated patients, did not require any further hospitalization due to pancreatitis. After surgery 2 patients claimed one recurrent

episode of abdominal pain each, which did not require hospitalization; and four patients had multiple abdominal pain episodes. Two of them had 1 hospitalization each. During the hospitalization they received a conservative treatment which was effective. Two other patients had revisions of the previous surgical procedure.

A total of 22 surgical interventions were performed in 20 patients. Two patients were initially operated at another institution and transferred post-operatively to our center for further management. One suffered from trauma and other received laparoscopic cholecystectomy due to gallstone disease.

A multimorbid patient with short bowel syndrome because of right hemicolectomy and near total small-bowel resection due to necrotizing enterocolitis had recurrent abdominal pain associated with: infection, fever and intrahepatic cholestasis due to choledochal cyst, bile duct stenosis and chronic pancreatitis. This patient received a combined surgery of hepaticoantrostomy and gastroduodenostomy. Primary goal was hepatico portojejunostomy, but due to the short bowel syndrome, that procedure was not possible. Four years later this patient came with the same symptoms. MRCP showed that the patient suffered from stenosis at his porto-antrostomy site which led to revision of hepaticoantrostomy.

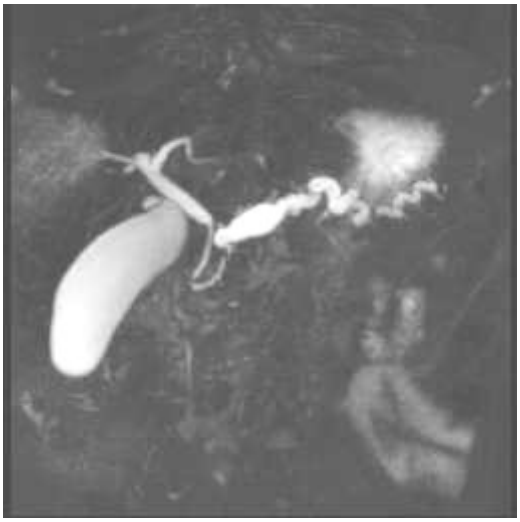

Figure 17: MRCP of chronic pancreatitis
(Courtesy of Medical University Graz)

Hepaticoantrostomy was the surgical treatment of choice in another patient with acute pancreatitis due to choledochal cyst and a common channel. This patient had a completely uneventful postoperative period.

Roux-en-Y hepaticojejunostomy and choledochal cyst resection were the surgical treatment of choice in 4 patients with chronic pancreatitis due to common channel and choledochal cyst. One of these patients needed a redo of hepatico-jejunostomy due to stenosis and recurrence of pancreatitis, 5 years after the primary surgery.

Side-to-side pancreaticojejunostomy (Puestow) was the surgery of choice in the patient with hereditary chronic pancreatitis (SPINK-1 mutation).

Roux-en-Y pancreaticojejunostomy was also the surgical treatment of choice in a patient with a long common channel. During the same operation, this patient underwent a duodenotomy because of duodenal atresia.

Because of a pancreatic necrosis in the frame of chemotherapy for Hodgkin lymphoma, had to undergo a surgical debridement and drainage of necrotic pancreas.

Laparoscopic cholecystectomy (n = 6) was the surgical treatment of choice in all patients with cholecystolithiasis complicated with acute pancreatitis due to temporary stone obstruction of papilla Vateri. Two patients reported that also members of their family have suffered from cholecystolithiasis.

ERCP and papillotomy was first performed at a patient with chronic pancreatitis due to a pancreas divisum, persistent ventral pancreas and sclerosis of papilla Vateri, but the condition of the patient wasn't getting much better so the surgical procedure - cholecystectomy and transduodenal papillosphincteroplasty was undertaken.

Acute pancreatitis associated with a gangrenous and perforated cholecyst led to a cholecystectomy in one patient.

Two patients with pancreatic tail rupture due to trauma needed a surgical treatment. One of these injuries was caused by a kick from a horse and the treatment consisted of resection of the pancreatic tail. The second injury was due to motorcycle accident and the treatment consisted of suturing of the pancreatic tissue, splenectomy and liver suturing. This patient received his emergency surgery at another institution, and was transferred to us postoperatively for further management.

Table 11: Surgical interventions	No
Cholecystectomy (Laparoscopic)	6
Cholecystectomy	2
Cholecystectomy and Transduodenal papillosphincterplasty	1
Roux-en-Y Hepaticojejunostomy (incl. 1 Revision)	5
Roux-en-Y Pancraticojejunostomy (Puestow)	2
Hepaticoantrostomy	1
Hepaticoantrostomy and Gastroduodenostomy (incl. 1 Revision)	2
Pancreasdebridement and drainage	1
Resection of the pancreas tail	1
Suture of the pancreas	1
Total number of surgical interventions	22

4.8 Follow-up

To evaluate the postoperative long-term outcome medical records were reviewed and a standardized questionnaire was determined.

Exocrine insufficiency was evaluated by the presence of steatorrhea or requirement for pancreatic enzyme supplementation. Endocrine insufficiency was evaluated on the basis of need for treatment of diabetes mellitus.

At the follow-up of 8 years and 5 months median (range 1 to 20 years) none of the 48 contacted patients reported any signs which would indicate endocrine or exocrine insufficiency of pancreas.

Out of 20 surgically treated patients, 14 patients could be reached, the follow-up period of 1 to 20 years (median, 7 years and 11 months). None of these patients needs any pancreatic medication or pain medication on regular basis. One patient reported the usage of Creon® in cases of excessive use of fatty foods and/or alcohol (at follow-up of 8 years). This patient had a laparoscopic cholecystectomy due to gallstone disease. Three patients regularly use other medications, due to other diseases such as Aktiferrin® because of idiopathic thrombocytosis and latent iron deficiency; Euthyrox® due to a hypothyroidism; and Movicol® due to chronic constipation. Seven patients decided not to drink alcohol, not to smoke and to avoid fatty meal. One patient is on fructose free diet.

Eleven patients, reported being completely pain free. Two patients reported mild episodes of recurrent pain, which aggravates with meals high in fat content. One of these two patients reported a discomfort in the area of the abdominal scar.

Growth delay was reported by 2 surgically treated patients.

One patient died in the follow-up period due to the multiorgan failure. This patient was multimorbid with extreme short-bowel syndrome and chronic hepatic insufficiency. Five surgically treated patients were lost to follow-up.

Out of 62 non-operative treated patients, 34 patients could be reached, the follow-up period of 2 to 20 years (median, 11 years and 3 months). Just one patient with recurrent pancreatitis (SPINK-1 mutation) reported occasionally to have abdominal pain. None of these patients needs any pancreatic medication. One patient needs

pancreatic diet. Four patients decided not to drink alcohol, not to smoke and to avoid fatty meal; one of them is also on a low protein diet.

Reduction of quality of life was reported in one case; and that due to Smith-Lemli-Opitz Syndrome. The same patient has growth delay and severe mental and physical disabilities.

Twenty-eight non-operative treated patients were lost to follow-up.

Except the child with severe mental and physical disabilities, all other operative and non-operative treated patients interviewed at follow-up returned to school and participate in normal daily activities.

5 Discussion

In the present study all hospitalized patients under the age of 18 with pancreatitis as one of the diagnoses at discharge from the Department of Pediatric and Adolescent Surgery of the Medical University of Graz were analyzed. Although pancreatitis in childhood is uncommon, it must be considered in every child with unexplained acute or recurrent abdominal pain [4].

Morinville et al [36] reported an increase in the total discharge diagnosis of acute pancreatitis from a low of 28 in 1993 to a high of 141 cases in 2004. Moreover Nydegger et al [37] also reported a significant increase in the annual incidence of pancreatitis. These reports do not find support in our data, which showed a decrease of patients admitted for treatment due to pancreatitis from a peak in 1996 to lower number of cases in 2010.

There is little published data on the duration of hospitalization or duration of illness in children with pancreatitis [9]. Median duration of hospital stay in our study was 14 days (range, 2 to 104 days). The underlying conditions, especially associated head trauma in trauma patients, affected the duration of hospital stay in our patient population. In addition, a number of patients with pancreatitis secondary to underlying surgical conditions other then pancreatitis also stayed in the hospital for a longer period of time to recover.

Our patients had an overall shorter hospital stay in direct comparison to Park et al [38] who observed a median duration of 19.5 days. The mean hospital stay reported by Benifla and Weizman was 15 days [8]. Pancreatitis is less common in infants and toddlers, and physicians are more likely to treat them conservatively [38].

The criterion for the diagnosis of the pancreatitis in this study was the threefold elevation of serum lipase (normal < – 205 U/l). Serum lipase levels were determined for all patients. This threshold of lipase elevation was observed in 87% of patients. Sixty-four percent of patients had both – amylase and lipase elevation.

Kandula et al [39] also observed that many of children diagnosed with pancreatitis had more then 3-fold elevated serum lipase and amylase levels. In contrast to our

study, the same threshold of both lipase and amylase elevation was noted in about 61%, and lipase elevation was noted in just 39% of children, in a study conducted by Kandula et al [39].

The discrepancy of 48% in lipase elevation between these two studies makes it clear that lipase elevation alone, which has greater sensitivity and specificity than amylase, is not sufficient to diagnose, thus additional criteria are required for diagnosis.

Similar to our study, Park et al [38] reported that US followed by CT were the most routine imaging techniques used in children with suspected pancreatitis. The practice of choosing US over the CT is reasonable because there is a greater risk of long-term complications with radiation exposure in infants, toddlers and children overall.

Twenty-two percent of our patients had MRI as well as MRCP. Both these imaging techniques gained in importance, especially in children because of no radiation exposure, non-invasive technique, and no need for contrast administration. In addition, using MRCP over the ERCP does not put children at risk for an additional episode of acute pancreatitis [17].

Once the diagnosis of pancreatitis, especially chronic pancreatitis is suspected, the anatomy of the pancreatic ductal system must be clearly defined with either ERCP or MRCP [40]. However, as described by Elmas [17] in a specific stage of pancreatitis each imaging technique has its own advantages and disadvantages such as in differentiating between acute and chronic pancreatitis, mild or severe acute pancreatitis, carcinoma and inflammatory masses, atrophy as the late feature of chronic disease, changes of the main pancreatic duct and side branches and other pancreatic abnormalities.

Pancreatitis in children varies markedly in etiology when compared with adults. While pancreatitis in adults is usually associated to alcohol abuse (80%) or gallbladder stones, in children the causes are more diverse [35].

In most cases seen in our institution, pancreatitis resulted from trauma, followed by the abnormalities of the biliary tree. The younger the patients the more common

the congenital disorders, and the older the patients the more common the traumatic causes.

Further etiologic causes included pancreatitis secondary to other diseases, systemic infection, hereditary, and idiopathic causes. While all 28 cases of trauma (27 blunt and one penetrating trauma), were responsible for one-time episode of acute pancreatitis, 58% chronic pancreatitis cases and even 66% of relapsing pancreatitis cases, were due to biliary tract disorders.

In addition, 8 cases of systemic infection were also responsible for one-time episode of acute pancreatitis. Both viral (EBV, Rotavirus) and bacterial (Campyulobacter jujuni, Staphylococcus aureus) infections were found in patients with otherwiese unclear cause of acute pancreatitis. These findings correlate with the published observation from Yachha et al [41].

Yachha et al [41] furthermore reported that trauma as the most common cause for pancreatitis, while idiopathic pancreatitis with 25% of cases was the second most common cause of pancreatitis in childhood. Similar data were also reported by Tiao et al [42] and by Wizman and Durie [43] with 20% and 25% of cases, where no cause was identified, respectively. This does not correlate with the data or the present study and may be explained with the fact that we assigned a diagnosis to any underlying infectious, systemic or biliary tract disease.

The biliary disease was responsible for 24% of all cases with pancreatitis in the present study. Most common causes for biliary tract disorders were cholecystolithiasis (45%), followed by common channel (30%), choledochal cyst (20%) and microlithiasis (5%). Even though cholecystolithiasis is uncommon in children [41] we had ten patients with gallstone pancreatitis, aged from 9 to 18 years. Two of them had a positive family history of cholecystolithiasis [44]. A high-fat Western diet is thought to be related with an increased risk of gallstone disease and may be a contributing factor [37]. Nydegger et al [37] reported that chronic high fat diet is associated with elevation of the pancreatic enzyme output, which may be sufficient to stress the pancreas in a genetically predisposed individual. Due to the retrospective character of the present study, we were not able to observe the effect of diet on the origin of pancreatitis in these children.

In our population, we had two cases of hereditary pancreatitis due to mutation in the SPINK-1, and one patient with pancreas divisum and SPINK-1 mutation. One of these children had three episodes of pancreatitis, and other two children have had multiple episodes of pancreatitis, leading to chronic pancreatitis. Individuals with mutations in the cationic trypsinogen gene (PRSS1), pancreatic secretory trypsin inhibitor gene (SPINK1), or the cystic fibrosis transmembrane conductance regulator gene (CFTR), are at an increase risk of developing acute or chronic pancreatitis [37].

We found that acute pancreatitis in our study was more common in males and older children. This is mainly due to trauma. In view of the rise of acute pancreatitis in adolescents, we conclude that in our study this was also mainly due to trauma and cases of pancreatitis secondary to other, which together make 74% of all acute cases in boys between 13 and 18 years of age.

The majority of patients in the present study were treated for a single episode of acute pancreatitis and the majority of patients were symptom free at the follow-up. Approximately one quarter of our patients needed surgical interventions. The goals of treatment in acute as well as chronic pancreatitis are pain relief, prevention or treatment of complications associated with pancreatitis, minimization or correction of endocrine and exocrine pancreatic activity or insufficiency [10,35].

Seventy-six percent of our patients received conservative treatment, including pain management with analgesics, antibiotics, pancreas diet, bowel rest and intravenous fluid administration. Twenty patients were surgically treated mainly because of the biliary tract disorders.

Simple surgical interventions consisting of cholecystectomy eliminated the cause of acute pancreatitis in 6 patients with gall-stone disease, who remained symptom free at 7 years and 4 months (median) follow-up.

Patients with anatomical abnormalities of the biliary tree, SPINK-1 mutation and trauma, required more sophisticated surgical procedures and thorough examination with multiple imaging modalities for diagnosis and treatment of the respective disorders. Most of these patients are also symptom free, at the

follow-up of 7 years and 11 months. One patient died during the follow-up period due to the severity of his associated diseases.

Longitudinal pancreaticojejunostomy which involves longitudinal section of the pancreas opening the main pancreatic duct to the lumen of a segment of jejunum by side to side anastomosis, was performed in one patient due to hereditary chronic pancreatitis, and in another patient with chronic pancreatitis due to anatomic anomalies of the biliary tree, respectively.

Andersen and Frey [45] observed the recurrence of pain in 30% of the patients within 3 to 5 years after longitudinal pancreaticojejunostomy (Puestow), but in our study none of these 2 patients reported recurrent symptoms at follow-up of 5 years and 12 years after a surgery, respectively. This procedure with generally excellent outcome [46], was also described by Jackson [16], Weber et al [34] and, Andersen and Frey [45] as the preferred method of decompression in pediatric patients with chronic pancreatitis, which in children is mainly the result of hereditary factors and/or aberrant pancreatic ductal drainage.

That is why the surgical intervention is a definitive treatment that addresses drainage of the entire major ductal system, and not ERCP which does not remove the fundamental cause of the poor drainage all through the entire pancreatic duct [35].

The management of pancreas divisum and sclerosis of papilla Vateri was papillosphincteroplasty. The same surgical procedure was also performed in 7 patients with pancreas divisum, in a study reported by Jackson [16]. Two patients from the same study, later underwent longitudinal pancreaticojejunostomy, having failed sphincteroplasty [16]. In our case there was no need for a second surgery. Our patient had just one recurrent episode. At a follow-up of 9 years and 10 months, no exocrine pancreatic insufficiency or diabetes was diagnosed.

Pancreatic necrosis may lead to secondary pancreatic infection, which is associated with high mortality. Jackson [16] reported a high mortality rate (24%) in patients with infected necrosis. On the other hand, he reported a death rate of 1.8% in sterile pancreatic necrosis. In order to prevent development of pancreatic

necrosis into pancreatic infection, debridement and drainage was performed in one patient.

According to our data (from medical charts as well as from the follow-up), surgical interventions have been shown to have a good short-term and long-term relief of pain and were associated with minimal morbidity and mortality.

Even though some patients had some episodes of pain after the surgery, this is not unexpected [47].

Pancreas diet or avoiding fatty meals diets can be administered until reaching symptom-free interval. In addition, reducing the restrictions for a normal daily life systematically, improves the quality of life of children and their families

Because the associated symptoms can be unclear and the pain difficult to localize in a distressed child, in addition to the rarity of pancreatic disease, the diagnosis of chronic pancreatitis in children is frequently delayed. This delay in diagnosis places the child through unnecessary pain, multiple hospitalizations, loss of days in school, significant psychosocial stressors, maladaptive behaviors, and endocrine and exocrine insufficiency [34,40].

In addition, most cases of acute pancreatitis in children, typically associated to trauma, infection, or medication use, are short-lived and seldom progress to chronic pancreatitis [34].

In order to prevent recurring attacks of acute pancreatitis, the patients should be placed on a low-fat diet, a regular exercise regime, and tight control of diabetes, with use of lipid-lowering drugs [12]. To avoid evolving of acute and relapsing pancreatitis to chronic pancreatitis laboratory controls of serum lipase and amylase, and ultrasound examination of the abdomen in children with positive history of pancreatitis should be regularly performed.

These steps are very important, and find support in study by Lankisch et al [48] who showed that long-term medical treatment of chronic pancreatitis is associated with diminished analgesic requirement after two decades of treatment, but at a cost of an almost universal endocrine dysfunction and permanent disability. In

contrast, surgical treatment of pancreatitis has been shown to eliminate pain and return patient to a normal quality of life [45].

The overall outcome of pancreatitis in children is better than in adults. Our death rate of 1% is far better than 27% reported by Buntain et al [49] in 1978, 21% by Weizman and Durie [43] in 1988 and 3% by DeBanto et al [50] in 2002, respectively. In the present study, the only death occurred as a result of complex underlying disease rather than from direct complications of pancreatitis.

We have shown that children treated for pancreatitis at a major pediatric referral center in Styria have an excellent long-term outcome at the median follow-up time of 9 years after pancreatitis.

In children, chronic and relapsing pancreatitis are far less common than acute pancreatitis. The reason for such number of cases with acute pancreatitis in comparison to chronic and relapsing pancreatitis is the increase of patients with trauma and pancreatitis secondary to other disease, particularly in adolescent male patients.

The surgical management of patients with chronic pancreatitis shows good long-term results in both, this and other published studies, respectively [34,35].

6 Conclusion

Though uncommon, pancreatitis in childhood is a demanding disease with the common need for surgical intervention mainly due to pancreatic duct obstruction caused by the underlying biliary tract disorder. Continuous long-term re-evaluation of the patients is needed to assure the success of surgical interventions and the patients' life quality.

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Appendix – Questionnaire

Follow-up examination

Need for routine check-up
0 – Yes
1 – No

Symptoms
0 – No
1 – Scar pain
2 – Stomach pain
3 – Stool/Bowel problems
4 - Other

Medication
0 – None
1 – Pancreas medication
2 – Medication because of other diseases
3 – 1+2

Diet
0 – None
1 – Pancreas diet
2 – Special diet – Gluten-free
3 – Other diet such as: No smoking, No alcohol, Avoidance of fatty foods

Reduction of quality of life
0 – None
1 – Yes – Due to St.p.Pancreatitis
2 – Yes – Due to other underlying disease

Growth reduction/delay
0 – Yes
1 – No

7. Current medical care
- Who looks after?
- How often
- The last control

8. Other diseases

Curriculum vitae

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