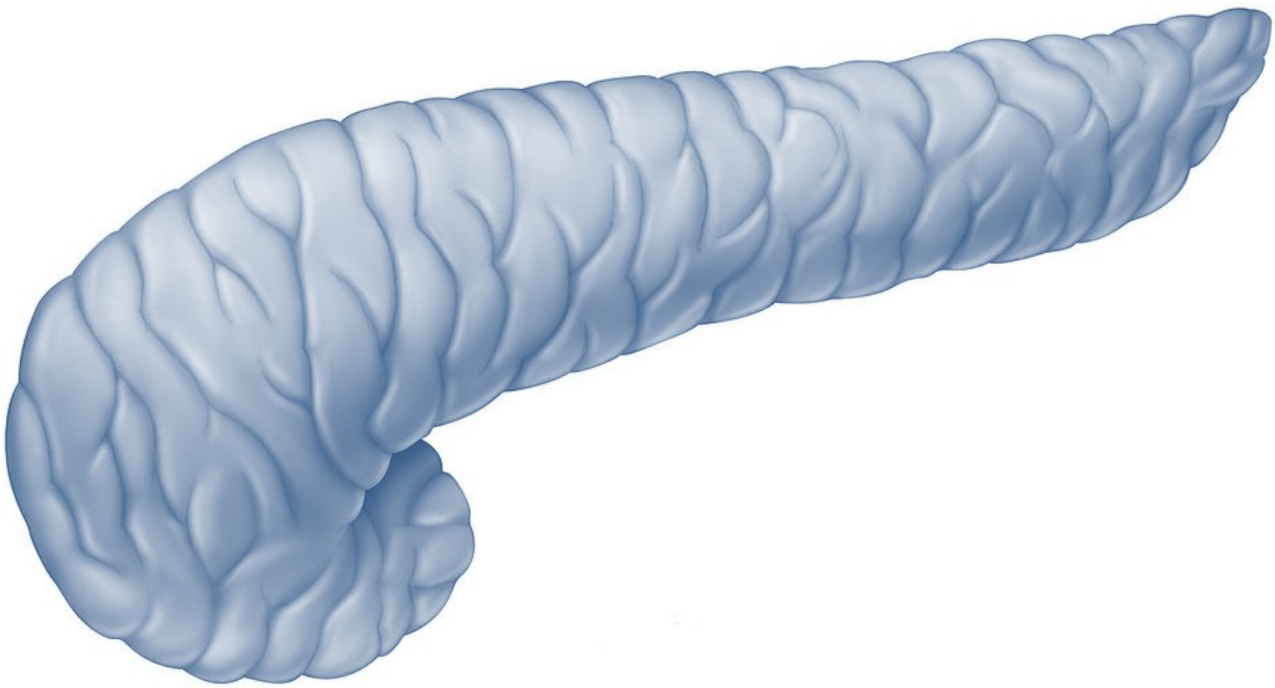

PANCREATIC DISEASES

Ljubljana, 2018

PANCREATIC DISEASES

Textbook of Selected Topics in Clinical Gastroenterology

Editor:
Rado JANŠA

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Editor: **Rado Janša**

Reviewers:
Vladka Salapura
Veronika Kralj-Iglič

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Person in Charge: **Borut Štabuc**

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EDITORIAL

Our society is becoming older and the lifespan of humans is getting longer with each decade. With age come struggles, problems and illnesses. However, age alone is not the reason why the number of certain illnesses and diseases in the so-called western civilization is rising. An unhealthy and stressful lifestyle – by too much eating, drinking, or smoking–, negative environmental influences, or genetics, are just some of the reasons why more and more people are getting sick.

Fact is; we are not listening to our own bodies. Pain is the body's way of telling us something is wrong. What starts as a pain or discomfort in the abdomen, can very likely be an early warning or sign for a serious illness. Some of those are connected with the pancreas. The number of pancreatic diseases is rising. Due to the inaccessibility of it, lying behind the stomach in front of the spine, surrounded by the intestines, liver, and gallbladder, the evaluation of pancreatic diseases is very difficult.

There are a number of disorders of the pancreas, the most common being acute, chronic or hereditary pancreatitis, and pancreatic cancer, which shown by recent studies is the fourth leading cause of death by cancer in Europe. If no actions are taken, it is set to become the second by the year 2020.

The purpose of the textbook is to present selected topics in clinical gastroenterology in connection with pancreatic diseases. From the most common to the rare. In addition, it presents multiple methods to evaluate the pancreas – from blood tests, physical evaluations to radiographic tests. The textbook presents new algorithms in diagnostics, endoscopic or surgical procedures and systemic treatments of pancreatic diseases.

However, that is not all. Particular attention is paid to the quality of life of patients suffering from pancreatic diseases, as well as their families and relatives trying to make everyday life easier – information about nutrition, pain management and psychiatric support.

I would like to express my deep gratitude to all participants for their contributions. I hope that this textbook will help to resolve open questions and encourage new research.

Rado JANŠA, Editor

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ACUTE PANCREATITIS

Jan Drnovšek*
University Medical Centre Ljubljana, Slovenia, Clinical Department of Gastroenterology

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ABSTRACT
Acute pancreatitis is an inflammatory disorder of the pancreas. It is an acute gastrointestinal disorder and is one of the leading gastroenterological causes of admission to hospital worldwide with its increasing incidence. The diagnosis of acute pancreatitis requires two of the following three features: sudden abdominal pain, elevated pancreatic enzymes values at least three times greater than the upper limit of normal and characteristic radiographic findings of acute pancreatitis. Acute pancreatitis can be subdivided into two types: interstitial oedematous pancreatitis and necrotising pancreatitis.
Management depends largely on severity of disease, which is defined by presence and duration of organ failure. Medical treatment of mild acute pancreatitis is symptomatic. Treatment of severe acute pancreatitis requires intensive care. Recognizing patients with mild and severe acute pancreatitis is crucial for achieving optimal outcomes, since severe acute pancreatitis is often related to increased mortality and morbidity.

Key words: *Acute pancreatitis, diagnosis, severity, complications*

INTRODUCTION

Pancreatitis is an inflammatory process in which pancreatic enzymes autodigest the gland. The gland sometimes heals without any impairment of function or any morphologic changes; this process is known as acute pancreatitis. Pancreatitis can also recur intermittently, contributing to the functional and morphologic loss of the gland; recurrent attacks are referred to as chronic pancreatitis.

Both forms of pancreatitis may present in the emergency department with acute clinical findings. Recognizing patients with severe acute pancreatitis as soon as possible is critical for achieving optimal outcomes. Management depends largely on severity and organ failure involvement (1).

PATHOPHYSIOLOGY

The pancreas is a secretory structure with an endocrine and an exocrine role. The endocrine part is composed of hormonal tissue distributed along the pancreas in discrete units called islets of Langerhans. The digestive enzymes of exocrine part drain into the duodenum. In normal pancreatic function, up to 15 different types of digestive enzymes are manufactured in the endoplasmic reticulum, targeted in the Golgi apparatus and packaged into zymogens as proenzymes. When a meal is ingested, the vagal nerves, vasoactive intestinal polypeptide, gastrin-releasing peptide, secretin, cholecystokinin and encephalins stimulate release of these proenzymes into the pancreatic duct.

In duodenum, the trypsinogen, which is the proenzyme of trypsin, is activated via hydrolysis of an N-terminal hexapeptide fragment by the brush border enzyme enterokinase. Trypsin then facilitates the conversion of the other proenzymes into their active forms (1, 2, 19).

A feedback mechanism exists to limit pancreatic enzyme activation after appropriate metabolism has occurred. It is hypothesized that elevated levels of trypsin, having become unbound from digesting food,

* Jan Drnovšek, MD
University Medical Centre Ljubljana, Slovenia, Clinical Department of Gastroenterology, Japljeva 2, SI–1000 Ljubljana.

lead to decreased cholecystokinin and secretin levels, thus limiting further pancreatic secretion.

Because premature activation of pancreatic enzymes within the pancreas leads to organ injury and pancreatitis, several mechanisms exist to limit this occurrence. First, proteins are translated into the inactive proenzymes. Later, posttranslational modification of the Golgi cells allows their segregation into the unique subcellular zymogen compartments. The proenzymes are packaged in a paracrystalline arrangement with protease inhibitors. Zymogen granules have an acidic pH and a low calcium concentration, which are factors that guard against premature activation until after secretion has occurred and extracellular factors have triggered the activation cascade. Under various conditions, disruption of these protective mechanisms may occur, resulting in intracellular enzyme activation and pancreatic auto digestion leading to acute pancreatitis (1, 2, 3, 19).

Acute pancreatitis may occur when factors involved in maintaining cellular homeostasis are out of balance. The initiating event may be anything that injures the acinar cell and impairs the secretion of zymogen granules; examples include alcohol use, gallstones and certain drugs. In addition, acute pancreatitis can develop when ductal cell injury leads to delayed or absent enzymatic secretion, as seen in patients with the *CFTR* gene mutation. Once a cellular injury pattern has been initiated, a cascade of cell injuries proceeds (1, 2). Lysosomal and zymogen granule compartments fuse, enabling activation of trypsinogen to trypsin

Intracellular trypsin triggers the entire zymogen activation cascade. Secretory vesicles are extruded across the basolateral membrane into the interstitium, where molecular fragments act as chemoattractants for inflammatory cells. Activated neutrophils exacerbate the inflamation by releasing superoxide or proteolytic enzymes (cathepsins B, D, and G; collagenase; and elastase). Finally, macrophages release cytokines that further mediate local and, in severe cases, systemic inflammatory responses. The early mediators defined to date are tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-8 (1–5).These mediators of inflammation cause an increased pancreatic vascular permeability, leading to hemorrhage, edema and pancreatic necrosis. As the mediators are excreted into the circulation, systemic complications can arise, such as bacteremia due to gut flora translocation, acute respiratory distresssyndrome (ARDS), pleural effusions, gastrointestinal (GI) hemorrhage and renal failure.

The systemic inflammatory response syndrome (SIRS) can also develop, leading to the development of systemic shock and multiorgan failure (see Table 3) (1-6,19).

Etiology

Long-standing alcohol consumption and biliary stone disease are the most common cause of acute pancreatitis, but numerous other etiologies are known. In 10–30% of cases, the cause is unknown, though studies have suggested that as many as 70% of cases of idiopathic pancreatitis are secondary to biliary microlithiasis.

Biliary tract disease

One of the most common causes of acute pancreatitis (accounting for approximately 40% of cases) is gallstones passing into the bile duct and temporarily lodging at the sphincter of Oddi. The risk of a stone causing pancreatitis is inversely proportional to its size (7).

It is thought that acinar cell injury occurs secondary to increasing pancreatic duct pressures caused by obstructive biliary stones at the ampulla of Vater, although this has not been definitively proven in humans. Occult microlithiasis is probably responsible for most cases of idiopathic acute pancreatitis (8).

Alcohol intake

Alcohol use is a major cause of acute pancreatitis, accounting for at least 35% of cases (9). At the cellular level, ethanol leads to intracellular accumulation of digestive enzymes, inducting their premature activation. At the ductal level, it increases the permeability of ductless, allowing enzymes to reach the parenchyma and cause pancreatic damage. Ethanol increases the protein content of pancreatic juice and decreases bicarbonate levels and trypsin inhibitor concentrations. This leads to the formation of protein plugs that block pancreatic outflow (4, 18).

Most commonly, the disease develops in patients whose alcohol ingestion is habitual over 5-15 years.

Occasionally, however, acute pancreatitis can develop in a patient with a weekend binging habit (10).

Post - endoscopic retrograde cholangiopancreatography pancreatitis

Pancreatitis occurring after endoscopic retrograde cholangiopancreatography (ERCP) is probably the third most common type, accounting for approximately 5 % of cases (11).

The risk of post-ERCP acute pancreatitis is increased if the endoscopist is inexperienced, if the patient is thought to have sphincter of Oddi dysfunction, or if manometry is performed on the sphincter of Oddi. Aggressive preintervention intravenous hydration has been durably shown to prevent post-ERCP pancreatitis in randomized studies. More recently, rectal indomethacin has been employed; it has been shown to reduce the incidence of post-ERCP pancreatitis and is now widely accepted at most institutions (4).

Abdominal trauma causes an elevation of amylase and lipase levels and in 1.5% cases clinical signs of pancreatitis. Pancreatic injury occurs more often in penetrating injuries than in blunt abdominal trauma. Blunt injury to the abdomen or back may crush the gland across the spine, leading to a ductal injury.

Drugs

Drug-induced pancreatitis is a relatively rare occurrence, accounting for approximately 2% of cases. Druge induced pancreatitis is usually mild. Drugs definitely associated with acute pancreatitis include the following: azathioprine, sulfonamides, tetracycline, valproic acid, didanosine, methyldopa estrogens, 6-mercaptopurine, pentamidine, 5-aminosalicylic acid and its compounds (1, 2).

Less common causes

The following causes each account for less than 1% of cases of pancreatitis.

Infection

Several infectious diseases may cause pancreatitis, especially in children. These cases of acute pancreatitis tend to be milder than cases of acute biliary or alcohol-induced pancreatitis.

Viral causes include mumps virus, coxsackievirus, cytomegalovirus, hepatitis virus, Epstein-Barr virus, echovirus, varicella-zoster virus, measles virus and rubella virus. Bacterial causes include *Mycoplasma pneumoniae, Salmonella, Campylobacter,* and *Mycobacterium tuberculosis.* Worldwide, *Ascaris* is a recognized cause of pancreatitis resulting from the migration of worms in and out of the duodenal papillae (1–3).

Hereditary pancreatitis

Hereditary pancreatitis is an autosomal dominant disorder related to mutations of the cationic trypsinogen gene (*PRSS1*). Mutations in this gene cause premature activation of trypsinogen to trypsin (1–3).

Hypercalcemia

Hypercalcemia from any cause can lead to acute pancreatitis. Causes include hyperparathyroidism, excessive doses of vitamin D, familial hypocalciuric hypercalcemia, and total parenteral nutrition (TPN). Routine use of automated serum chemistries has allowed earlier detection and reduced the frequency of hypercalcemia manifesting as pancreatitis (2).

Developmental abnormalities of pancreas

There are two developmental abnormalities commonly associated with pancreatitis: pancreas divisum and annular pancreas.

Pancreas divisum is a failure of the dorsal and ventral pancreatic ducts to fuse during embryogenesis. It occurs in approximately 5% of the population. It appears that the presence of stenotic minor papillae and an atretic duct of Santorini are additional risk factors that together contribute to the development of acute pancreatitis through an obstructive mechanism (1-4).

Hypertriglyceridemia

Clinically significant pancreatitis usually does not occur until a person's serum triglyceride level reaches 1000 mg/dL. It is associated with type I and type V hyperlipidemia. Although this view is somewhat controversial, most authorities believe that the association is caused by the underlying derangement in lipid metabolism rather than by pancreatitis causing hyperlipidemia. This type of pancreatitis tends to be more severe than alcohol- or gallstone-induced disease (1–4).

Tumors

Obstruction of the pancreatic ductal system by a pancreatic ductal carcinoma, ampullary carcinoma, islet cell tumor, solid pseudotumor of the pancreas, sarcoma, lymphoma, cholangiocarcinoma or metastatic tumor can cause acute pancreatitis. The chances of pancreatitis occurring when a tumor is present are approximately 14%. Pancreatic cystic neoplasms, such as intraductal papillary-mucinous neoplasm (IPMN), mucinous cystadenoma, or serous cystadenoma, can also cause pancreatitis (1–4).

Toxins

Exposure to organophosphate insecticide can cause acute pancreatitis.

Surgical procedures

Acute pancreatitis may occur in the postoperative period of various surgical procedures. Postoperative acute pancreatitis is often a difficult diagnosis to confirm and it has a higher complication rate than pancreatitis associated with other etiologies.

Autoimmune pancreatitis

Autoimmune pancreatitis, a relatively newly described entity, is an extremely rare cause of acute pancreatitis with its estimaded prevalence of 0.82 per 100.000 individuals. The mechanism remains unclear, it is thought to be related with inappropriate immune response.

EPIDEMIOLOGY

Worldwide, the incidence of acute pancreatitis ranges between 5 and 80 per 100.000 population. Generally, acute pancreatitis affects males more often than females (3). The trend in rising incidence has been recognized over the past several decades. The median age at onset depends on the etiology. The median age of onset differs for various etiologies: alcohol-related - 39 years, biliary tract–related - 69 years, trauma related - 66 years, drug induced – 42 years, post ERCP - 58 years (12).

Diagnosis

The diagnosis of acute pancreatitis requires two of the following three features:

(1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiatingto the back);

(2) serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal;

(3) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) and less commonly magnetic resonance imaging (MRI) or transabdominal ultrasonography.

The onset of acute pancreatitis is defined as the time of onsetof abdominal pain and not the time of admission to the hospital (13).

Different strategies have been used to assess the severity of acute pancreatitis and predict outcome. Several clinical scoring systems (e.g, Ranson criteria, Glasgow, Imrie) are available. The APACHE II scoring system, though cumbersome, appears to be the best validated (13, 20, 21).

Acute pancreatitis can be subdivided into two types: interstitial oedematous pancreatitis and necrotising pancreatitis.

Interstitial oedematous pancreatitis

The majority of patients with acute pancreatitis have diffuse (or occasionally localised) enlargement of the pancreas due to inflammatory oedema. On contrast enhanced computer tomography (CECT), the pancreatic parenchyma shows relatively homogeneous enhancement and the peripancreatic fat usually shows some inflammatory changes of haziness or mild stranding. There may also be some peripancreatic fluid. The clinical symptoms of interstitial oedematous pancreatitis usually resolve within the first week (13).

Necrotising pancreatitis

About 5–10% of patients develop necrosis of the pancreatic parenchyma, the peripancreatic tissue or both. Necrotising pancreatitis most commonly manifests as necrosis involving both the pancreas and peripancreatic tissues and less commonly as necrosis of only the peripancreatic tissue, and rarely of the pancreatic parenchyma alone. The impairment of pancreatic perfusion and signs of peripancreatic necrosis evolve over several days, which explains why an early CECT may underestimate the eventual extent of pancreatic and peripancreatic necrosis. Patients with peripancreatic necrosis alone have increased morbidity and intervention rates compared to patients with interstitial oedem-

atous pancreatitis. The natural history of pancreatic and peripancreatic necrosis is variable, because it may remain solid or liquefy, remain sterile or become infected, persist, or disappear over time (13).

DEFINITION OF SEVERITY OF ACUTE PANCREATITIS

The determinant of the severity of acute pancreatitis during the early phase is primarily the presence and duration of organ failure. This is described as "transient organ failure" if the organ failure resolves within 48 h or as "persistent organ failure" if organ failure persists for >48 h. If organ failure affects more than one organ system, it is termed as multiple organ failure (MOF). Although local complications may be identified during the early phase, they are not the predominant determinants of severity.

Three organ systems should be assessed to define organ failure: respiratory, cardiovascular and renal. Organ failure is defined as a score of 2 or more for one of these three organ systems using the modified Marshall scoring system, shown in table 1 (13).

This classification defines three degrees of severity: mild acute pancreatitis, moderately severe acute pancreatitis and severe acute pancreatitis (see Table 1). Terminology that is important in this classification includes transient organ failure, persistent organ failure, and local or systemic complications (13).

Mild acute pancreatitis

Mild acute pancreatitis is characterized by the absence of organfailure and the absence of local or systemic complications. Patients with mild acute pancreatitis will usually be discharged during the early phase. Patients with mild acute pancreatitis usually do not require pancreatic imaging, and mortality is very rare (13).

Moderately severe acute pancreatitis

Moderately severe acute pancreatitis is characterized by the presence of transient organ failure or local or systemic complications in the absence of persistent organ failure. An example of a symptomatic local complication is a peripancreatic collection resulting in prolonged abdominal pain, leucocytosis and fever (13).

- ➔Mild acute pancreatitis
  - ➔No organ failure
  - ➔No Local or systemic complications
- ➔Moderatley severe acute pancreatitis
  - ➔Organ failure that resolves within 48h (transient organ failure) and/or
  - ➔Local or systemic complications without persistant organ failure
- ➔Severe acute pancreatitis
  - ➔Persistent organ faliurew (>48h)
    - ➔Single organ failure
    - ➔Multiple organ failure

Table 2: *Grades of severity* (13).

	Score				
Organ system	**0**	**1**	**2**	**3**	**4**
Respiratory (PaO_2/FiO_2)	>400	301–400	201–300	101–200	≤101
Renal*					
(serum creatinine, μmol/l)	≤134	134–169	170–310	311–439	>439
(serum creatinine, mg/dl)	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9
Cardiovascular (systolic blood pressure, mm Hg)†	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH<7.3	<90, pH<7.2
For non-ventilated patients, the FiO_2 can be estimated from below:					
Supplemental oxygen (l/min)	**FiO_2 (%)**				
Room air	21				
2	25				
4	30				
6–8	40				
9–10	50				

A score of 2 or more in any system defines the presence of organ failure.
*A score for patients with pre-existing chronic renal failure depends on the extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine ≥134 μmol/l or ≥1.4 mg/dl.
†Off inotropic support.

Table 1: *Modified Marshall scoring system for organ dysfunction* (13).

Severe acute pancreatitis

Severe acute pancreatitis is characterized by persistent organ failure. Organ failure that develops during the early phase is set in motion by the activation of cytokine cascades resulting in signs of Sistemic inflammatory response syndrome (SIRS) (Table 3). When SIRS is present and persistent, there is an increased risk that the pancreatitis will be complicated by persistent organ failure, and the patient should be treated as if they have severe acute pancreatitis. Persistent organ failure may be single or multiple organ failure.

Patients with persistent organ failure usually have one or more local complications. Patients who develop persistent organ failure within the first few days of the disease are at increased risk of death, with a mortality reported to be as great as 36–50% (13, 22)

SIRS – defined by presence of two or more criteria:

- ➔Heart rate >90 beats/min
- ➔Core temperature $<36^0$C or $>38^0$C
- ➔White blood cound <4.000 or >12.000/mm^3
- ➔Respiration >20/min or PCO_2 <32 MM Hg[13]

Table 3: *Signs of systemic inflammatory response syndrome* (13).

TREATMENT

Patients with acute pancreatitis lose a large amount of fluids to third spacing into the retroperitoneum and intra-abdominal areas. Therefore, prompt intravenous hydration is required within the first 24 hours (250–500mL/h). Analgesics are administered for pain relief. After withdrawal of per mouth feeding, the following should be started as soon as possible in the absence of abdominal pain and vomitus (4, 14).

If the cause of pancreatitis is believed to due to choledocholithiasis, ERCP should be performed in 24 hours after admission. In case of biliary pancreatitis with spontaneous gallstone resolution, cholecystectomy should be performed during the same hospital admission (22). In case of suspicion, an endoscopic ultrasound or MRCP can be proceded (2). Acute hyperlipemic pancreatitis with elevated serum triglyceride level requires plasmapferesis (15). Patients with severe acute pancreatitis require intensive care to be provided with best supportive care.

Most of the peripancreatic fluid collections, which last over four weeks, can be followed clinically. However, when they are symptomatic, infected or larger than 7 cm and are rapidly expanding in an acutely ill patient, intervention is required. Several different therapeutic approaches may be implemented, including percutaneous, endoscopic or surgical approaches. In case of infected peripancreatic fluid collections, antibiotic treatment is indicated.

COMPLICATIONS

Local complications

Local complications are acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and walled-off necrosis (see Table 4).

Acute peripancreatic fluid collection	Usually develops in the early phase of interstitial oedematous pancreatitis, it is confined by fascia of the retroperitoneum, may be multiple, mostly remain sterile and usually resolve spontaneously without intervention.
Pancreatic pseudocyst	It is a delayed (usually >4 weeks) complication of interstitial oedematous pancreatitis, surrounded by a well-defined wall. It arises from disruption of the main pancreatic duct or its intra-pancreatic branches without any recognisable pancreatic parenchymal necrosis. When there is evident solid necrotic material within the cavity, the term pseudocyst should not be used.
Acute necrotic collection	Appears during the first 4 weeks and contains variable amounts of fluid and necrotic tissue involving the pancreatic parenchyma and/or the peripancreatic tissues.
Walled-off necrosis	This maturation occurs usually after 4 weeks after onset of necrotising pancreatitis. It consists of necrotic pancreatic and/or peripancreatic tissue and has a well-defined inflammatory wall.

Table 4: *Definition of pancreatic and peripancreatic collections* (13).

Other local complications of acute pancreatitis include gastric outlet dysfunction, splenic and portal vein thrombosis, and colonic necrosis. Local complications should be suspected when there is persistence or recurrence of abdominal pain, secondary increases in serum pancreatic enzyme activity, increasing organ dysfunction, and/or the development of clinical signs of sepsis, such as fever and leucocytosis (3, 4 13).

Infected pancreatic necrosis

Pancreatic and peripancreatic necrosis can remain sterile or become infected; most of the evidence suggests no absolute correlation between the extent of necrosis and the risk of infection and duration of symptoms. Infected necrosis is rare during the first week. The diagnosis of infected pancreatic necrosis is important because of the need for antibiotic treatment and likely active.

Intervention (13, 16). The presence of infection can be presumed when there is extraluminal gas in the pancreatic and/or peripancreatic tissues on CECT or when percutaneous, image-guided, fine-needle aspiration (FNA) is positive for bacteria and/or fungi on Gram stain and culture. The development of secondary infection in pancreatic necrosis is associated with increased morbidity and mortality (13, 17).

Systemic complications

Exacerbation of pre-existing co-morbidity, such as coronary artery disease or chronic lung disease, precipitated by the acute pancreatitis is defined as a systemic complication. In this document, we distinguish between persistent organ failure (the defining feature of severe acute pancreatitis) and other systemic complications, which are an exacerbation of pre-existing co-morbid disease (1, 2, 4, 13).

CONCLUSION

Acute pancreatitis is being a serious medical condition, which often related to increased mortality and morbidity. After setting the right diagnosis, prompt treatment should be started.

All patients with acute pancreatitis should be hospitalized. Management depends largely on severity of disease.

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PANCREATIC DISEASES

Textbook of Selected Topics in Clinical Gastroenterology

CHRONIC PANCREATITIS

Luka Strniša*
University Medical Centre Ljubljana, Slovenia, Clinical Department of Gastroenterology

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ABSTRACT
Chronic pancreatitis is a disease of constant or recurrent pancreatic inflammation of various aetiologies which leads to fibrosis of pancreas and loss of pancreatic exocrine end endocrine function with malabsorption and diabetes. This process is accompanied with acute exacerbations of inflammation similar to acute pancreatitis. The most common symptom of chronic pancreatitis is chronic abdominal pain which however is variable and does not correlate with the level of inflammation and loss of function of pancreas. The disease has a severe influence on quality of life and mortality. The diagnosis may be difficult in the early stages of the disease. The treatment must be multidisciplinary and include in most cases therapy of alcohol and tobacco dependence.

Key words: *Chronic pancreatitis, autoimmune pancreatitis, hereditary pancreatitis, idiopathic pankreatitis, endoscopic therapy, pancreatic exocrine insufficiency*

WHAT IS CHRONIC PANCREATITIS

Chronic pancreatitis is a disease of constant or recurrent inflammation of the pancreatic parenchyma of various ethiologies leading to a fibrotic transformation of the organ with loss of exocrine and endocrine functions with resulting malabsorption and diabetes. These events can be accompanied by acute exacerbations of inflammation that are very similar to acute pancreatitis. The most common symptom of chronic pancreatitis is chronic abdominal pain which however is variable and does not correlate with the level of inflammation and loss of function of pancreas. The disease has a severe influence on quality of life and mortality.

EPIDEMIOLOGY

Chronic pancreatitis of all ethiologies combined has an incidence of 5–10 / 100,000 and a prevalence of 120 / 100,000 inhabitants. The incidence varies and is correlated with the average amount of alcohol consumed (1). Mortality is increased 3–4x compared to the population without chronic pancreatitis, with 70% survival after 10 years and 45% survival after 20 years. The continued use of alcohol is associated with worse survival (2, 3). 40% of patients with chronic pancreatitis are not employed or are retired with disability as a result of the disease or alcoholism.

ETIOLOGY

Alcohol is a causative factor for the emergence of chronic pancreatitis in 50–84% of cases. It is estimated that consumption of at least 80g of alcohol per day for at least 6–12 years, regardless of the type of alcohol. However less than 5% of these excess alcohol drinkers develop chronic pancreatitis (4), the reason probably being the presence of other environmental and genetic factors. Smoking is an independent risk factor and leads to a faster progression of the disease, even when alcohol consumption is stopped. It is associated with worsening of pain and calcification of the pancreas. Long-term smoking is also associated with an increased risk of developing chronic pancreatitis even without alcohol intake (5).

* Luka Strniša, MD
University Medical Centre Ljubljana, Slovenia, Clinical Department of Gastroenterology, Japljeva 2, SI–1000 Ljubljana.

Primary hyperparathyroidism (pHPT) is associated with acute and chronic pancreatitis – only 1% of patients with pancreatitis have a pHTP, but 12% of patients with pHTP have chronic pancreatitis, with or without body calcifications.

Mutations N29I and R128H in the trypsinogen gene (SPINK1) are present in two thirds of hereditary pancreatitis with 80% penetrance and AD inheritance. Hereditary pancreatitis represents less than 0.3% of the prevalence of chronic pancreatitis (6) and typically becomes symptomatic before age 20.

Idiopathic (sporadic) chronic pancreatitis accounts for up to 28% of all cases of chronic pancreatitis. With 45% of this type of CP, genetic risk factors that greatly increase the likelihood of developing chronic pancreatitis are found (PRSS1, CPA1, CFTR, CTCR, CEL). Some genetic risk factors are also more common in alcoholics who develop alcoholic pancreatitis.

Chronic pancreatitis is not correlated with cholecystolithiasis or choledocholithiasis. Patients with hypertriglyceridemia may rarely develop chronic pancreatitis.

Chronic obstruction of the pancreatic duct may cause chronic pancreatitis proximal to the obstruction. The obstruction may be due to benign or malignant tumours, possibly even after a severe attack of acute pancreatitis with ductal disruption, usually in association with necrotic collections. In most cases of chronic pancreatitis protein precipitates form in the ducts which can be calcifed and cause obstruction. 'Pancreas divisum' is an anatomical variant, in which there is no association between the ventral (main - Wirsung) and the dorsal (accessory - Santorini) part of the pancreatic duct. This variant is present in 5–10% of people and is likely a factor in the development of chronic pancreatitis in the presence of other risk factors.

Tropical pancreatitis is a common form of chronic pancreatitis in the tropical and subtropical regions of Asia. There are no clear criteria for separation from other types of idiopathic pancreatitis. As with idiopathic pancreatitis, genetic risk factors have been identified.

Pancreatitis in childhood is associated with certain syndromic genetic disorders, most commonly cystic fibrosis.

Autoimmune pancreatitis (AIP) includes two subtypes of chronic fibrotic inflammation of the pancreas that are responsive to steroid therapy. It represents up to 5% CP incidence.

Subtype I AIP represents 4–6% of all chronic pancreatitis. It is a chronic inflammation of the pancreas, which in 60% is accompanied by the involvement of other organs. In addition to pancreatic disorder, the systemic inflammatory process can usually involve the bile ducts, salivary glands, kidneys, retroperitoneum and lymph nodes. In the affected organs a lymphoplasmocytic infiltratate with numerous IgG4-positive inflammatory malformations (more than 10 cells per apparent field) is present. Serum IgG4 levesa are often elevated. We can talk about the pancreatic manifestation of 'IgG4 related disease'. A typical histological picture of lymphoplasmocytic sclerosing pancreatitis develops in the pancreas.

Subtype 2 AIP is less common. In this AIP subtype, IgG4 levels and concurrent disorders of other organs are not present. The diagnosis can only be confirmed patohystologically. AIP type II is more common in patients with chronic inflammatory bowel disease.

In autopsies, a fibrotic pancreatic restructuring can often be found in patients who did not have clinical images of chronic pancreatitis. Asymptomatic pancreatic fibrosis is common in chronic alcoholics, at advanced age, and in patients with advanced renal disease and diabetes. Because of this, only histological criteria are not sufficient for the diagnosis of chronic pancreatitis.

PATHOGENESIS

The pathogenesis of CP is not fully understood and has several factors. The first factor is the reduction of the bicarbonate secretion due to genetic factors, alcohol or mechanical obstruction. Another factor is the intraparenchymal activation of digestive enzymes, also due to genetic factors in combination with the influence of environmental factors (smoking and alcohol). Protein precipitates with secondary calcifications that lead to ductal hypertension and acinar atrophy

precipitate in pancreatic ducts. Increased pressure in the gland can cause chronic ischemia. The formation of free radicals, the level of which is increased with smoking and alcoholism, is increased.

CLASSIFICATION

Several different clinical / functional / morphological scores and classifications (Manchester, Rosemont, ABC, M-ANNEHEIM) are available and can be used to divide the disease into stages. They are rarely used. The latest European guidelines conclude that prospective validations of these scoring systems and their inclusion in therapeutic schemes are required.

CLINICAL PICTURE

Chronic pancreatitis can present clinically in the form of recurrent acute attacks of pancreatitis (acute exacerbations of CP) and/or permanent pancreatic type pain. With the gradual destruction of the gland, malabsorption of nutrients occurs due to the exocrine insufficiency and diabetes due to endocrine insufficiency. Biliary or duodenal obstruction because of mass effect of occur. Thrombosis of splenic or portal vein can occur with resulting symptoms of portal hypertension.

Acute exacerbations

The first symptoms of chronic alcoholic pancreatitis are most frequently recurrences of acute alcoholic pancreatitis. Already at this point, most patients have histological signs of chronic pancreatitis, but up to 40% of patients will not develop a clinical picture of chronic pancreatitis with exocrine and endocrine insufficiency. The attacks are the result of prolonged and not short-term excessive alcohol consumption (7). Other forms of chronic pancreatitis are also often accompanied by acute exacerbations, which are clinically identical to the acute attack of non-chronic (e.g. biliary) pancreatitis. However, some patients with chronic pancreatitis have no acute exacerbations.

Chronic pain

In most patients with chronic pancreatitis the main symptom is chronic abdominal pain, which may be episodic or almost constant. It is mostly located in the epigastrium with radiation in the back, often accompanied by the nausea. Pain is often worse after meals and at night, consequently, patients are afraid to eat. The pain often changes with time. It typically occurs at intervals that last for a few days, weeks or months, and then ceases without a clear cause. Both pain-free intervals and painful intervals are unpredictable and uneven, so the management of a patient with chronic pancreatitis is individual. Most studies have described a slow decrease in pain levels during disease progression in at least half of patients. In some patients the pain remits completely, usually in the advanced stage of the disease with of pancreatic insufficiency and in the presence of calcination (8, 9). Some patients with CP do not have chronic pain - 10% develop chronic pancreatitis with pancreatic insufficiency without any pain symptoms.

Chronic pain is partially caused by increased pressure in the pancreatic ductal system because of obstruction. Patients with signs of ductal obstruction on imaging have a greater likelihood of a response to endoscopic or surgical drainage therapy. However, a large proportion of patients with chronic pain have no signs of obstruction of the ducts (8, 10–12). The second etiology of pain is neurogenic because of direct activation of nociceptive pathways and central reinforcement. Therefore, chronic pancreatic pain can persist even after total pancreatectomy.

Idiopathic chronic pancreatitis occurs in two subtypes - an early type, presenting in the 2nd and 3rd decade; and late type – presenting in the 6–7 decade. The early subtype has a typical presentation with chronic pain and a very slow development of calcination and pancreatic insufficiency which develop over more than 20 years. Most patients will need surgery because of pain and local complications.

In the late subtype of idiopathic pancreatitis, pain is less pronounced and frequent, while calcination and exocrine and endocrine pancreatic insufficiency develop faster and is the presenting feature in 20% of cases.

Pancreatic exocrine Insufficiency (PEI)

Is a reduction in the excretion of pancreatic enzymes and bicarbonate. For steatorrhea, the amount of secreted digestive enzymes must be reduced by 90-95%, therefore this symptom occurs only in the advanced stage of chronic pancreatitis, usually 10–20 years after the first symptoms of CP. The consequence of PEI is malnutrition (which may be present long before steatorrhea) and other abdominal symptoms (diarrhoea, meteorism, pain).

Diabetes

In the advanced stage chronic pancreatitis also results in endocrine pancreatic insufficiency, which is more common after operative therapy and in tropical type pancreatitis. After long follow-up (25 years), diabetes develops 40–83% of patients (9, 13). Concurrent with insulin deficiency, there is also a deficiency of glucagon secretion which is why patients are at an increased risk of severe and prolonged hypoglycaemias (DM subtype IIIc).

Other complications:

Pseudocysts are pancreatic or peri-pancreatic fluid collections with a high content of pancreatic enzymes without necrosis. They develop frequently in CP, commonly after acute exacerbations. They may rarely communicate with the main pancreatic duct. Larger collections may cause gastric outlet obstruction and biliary obstruction with hyperbilirubinemia. They may also cause sepsis after becoming infected. Spontaneous perforations are possible into the peritoneal cavity or the intestine. A fistula in the pleura can form with resulting chronic pleural effusion and dyspnoea. Acute bleeding into the pseudocyst is also possible.

With chronic inflammation and fibrosis of the pancreas, the volume of the pancreatic head may increase. This inflammatory tumour can also cause obstruction of the duodenum or biliary system.

Acute haemorrhage with bleeding from gastric varices may occur after portal hypertension develops with splenic or portal vein thrombosis. Very rarely, arterial haemorrhage from erosion of splenic artery with pseudo-aneurysm formation can occur.

The incidence of pancreatic cancer is elevated up to 13x with 4% lifetime risk. Patients with hereditary pancreatitis have an even greater risk (69x relative risk), especially if they smoke. Four out of ten patients with chronic hereditary pancreatitis will develop pancreatic cancer.

Hereditary pancreatitis (HP)

A strict definition is used by the European Register of Hereditary Pancreatitis and Family Pancreatic Cancer (EUROPAC); the HP patient should have at least two first degree or three second degree relatives of two or more generations with chronic pancreatitis of unexplained cause. When a patient has relatives with idiopathic pancreatitis but does not meet the above criteria, he should be classified as having familiar idiopathic pancreatitis.

Hereditary pancreatitis begins with recurrent episodes of acute pancreatitis, usually in childhood or adolescence, but may first appear in young adults. The course of these acute episodes is in no way different from acute pancreatitis of other causes. The patients develop recurrent epigastric pain. Patients usually have two to four exacerbations a year. The chronic pancreatitis which develops is indistinguishable clinically from early idiopathic chronic pancreatitis.

Autoimmune pancreatitis

The most common clinical presentation of AIP is obstructive jaundice, with or without pain and elevated levels of pancreatic enzymes. A pancreatic inflammatory cell infiltrate is present in the pancreas, which on imaging takes form of a solitary pancreatic tumour or a diffusely enlarged pancreas. The pancreatic duct may have long stricture without significant proximal dilatation. In the chronic phase of the disease, pancreatic exocrine and endocrine insufficiency occurs. Calcination is observed rarely and only after prolonged illness.

In subtype I, signs of other organ involvement can also be detected (bile ducts, salivary glands, kidneys, retroperitoneal organs and lymph nodes). Thus, the pancreatic disorder can be accompanied by urethral and biliary strictures, lymphadenopathy, sclerosing sialoadenitits, retroperitoneal fibrosis, and tubulointerstitial nephritis. The involvement of other organs may occur before, at the same time or after the onset of pancreatic disease. Stenosis of bile ducts has the same image appearance as in primary sclerosing cholangitis (PSC) but are responsive to steroid therapy.

In subtype I, the incidence for men is twice that of women. The patients are usually older than 50, usually between the ages of 60 and 70, but the presentation is also possible earlier. Subtype 2, which is less common, is equally common in both sexes and the incidence is at 50 years old. Both subtypes clinically frequently mimic the symptoms of pancreatic cancer.

DIAGNOSIS

Chronic pancreatitis is a slow-moving disease. Diagnostic tests can detect changes in exocrine pancreatic function and changes in the structure of the gland, which are rarely present in the initial phase of the disease when fibrosis and inflammation are already clearly visible on histological samples (which in practice are almost never available). Serum laboratory tests are normal except in acute exacerbations. Most patients have symptoms long before the diagnosis which requires a combination of clinical images with image tests and functional tests.

To establish the diagnosis, M-ANNHEIM diagnostic criteria can be used to determine the likelihood of the presence of chronic pancreatitis. In addition to a typical clinical picture of chronic pancreatitis (recurrent acute pancreatitis or chronic abdominal pain), at least one criterion should be present:

Proven chronic pancreatitis (one or more criteria)

- ➔calcination in the pancreas;
- ➔moderate or significant changes in pancreatic ducts on imaging (according to the Cambridge classification);
- ➔severe pancreatic exocrine insufficiency corrected with enzyme replacement therapy
- ➔a typical histological picture.

Probable chronic pancreatitis (one or more criteria)

- ➔mild changes in pancreatic ducts (according to the Cambridge classification);
- ➔recurrent or persistent pseudocysts
- ➔pathological test for pancreatic exocrine insufficiency (e.g. faecal elastase);
- ➔endocrine insufficiency (e.g. pathological glucose tolerance test).

Possible chronic pancreatitis

- ➔clinical picture without other criteria of morphological or functional changes.

Pancreatic function tests

Direct pancreatic function tests measure the secretion of pancreatic enzymes into the duodenum after stimulation with CCK / secretin. They are the most sensitive tests and are closest to a gold standard for diagnosis. Unfortunately, there are invasive, time-consuming and are not used in clinical practice. Indirect tests measure pancreatic enzymes in faeces. The measurement of the amount of fat in a 3-day faces collection along a standard diet is sensitive but is in practice difficult to implement. The qualitative analysis of a single sample of faeces for fat content strongly depends on the amount of fat consumed and is only positive in patients with already developed steatorrhea.

Measurement of elastase in a sample of faeces is commonly used and reliably detects advanced pancreatic exocrine insufficiency but is poorly sensitive for mild forms. Low levels can also be seen with diarrhoea and bacterial overgrowth of the small intestine. The precision of the test is better than the measurement of chymotrypsin in faeces. The C13 breath test with mixed triglycerides has good sensitivity and specificity but is very time consuming to perform. Guidelines (14, 15) recommend performing a faecal elastase test at a clinical suspicion of CP and when CP is diagnosed since the clinical signs of PEI are unreliable (see Table 1).

Imaging

The first imaging study on suspected CP is usually an abdominal ultrasound, which has relatively poor sensitivity and can only demonstrate CP in the advanced stage. EUS, MRI/MRCP, CT and

Table 1

	Mild PEI	**Moderate PEI**	**Severe PEI**	
	senzitivnost	senzitivnost	senzitivnost	
Feacal elastase	54%	75%	95%	85%
Faecal chimotrypsine	<50%	60%	80/90%	70%
Faecal fat content	0%	0%	78%	70%
C13 breath test	62-100%		90-100%	80-90%

ERCP have much better diagnostic reliability. The best diagnostic tests are EUS and ERCP. ERCP is no longer used for diagnostic purposes due to the significant potential for complications of the investigation. EUS is the most reliable investigation in the initial stage of the disease, especially with the use of the EUS classifications for chronic pancreatitis. EUS is also the useful for screening patients with significantly increased risk of cancer as with hereditary pancreatitis. In the presence of chronic pancreatitis, the characterization of lesions in the tissue is very difficult - EUS with FNA has the highest (but still relatively poor) sensitivity for pancreatic cancer (50–75%) in chronic pancreatitis, which is slightly better than MRI / MRCP. Using contrast and elastography, the EUZ has the potential to improve diagnostic accuracy.

	Sensitivity for CP	Specificity for CP
CT	/	/
ERCP	70-80%	80-100%
MRCP	88%	98%
Abdominal US	60-81%	70-97%
Endoscopic US (EUS)	80-100%	80-100%

Based on the above, European guidelines recommend abdominal ultrasound as the initial investigation. In case of a non-conclusive investigation and the persistence of the clinical suspicion of CP a EUS should be performed. CT and MRI are complementary investigations. When evaluating imaging findings classification schemes should be used (e.g. Cambridge criteria)

Evaluation of etiology

At diagnosis chronic pancreatitis, it is necessary to search for the etiology. Patients should be evaluated for alcohol consumption (with a standardized questionnaire and CDT measurement) and smoking. Hyperlipidaemia and primary hyperparathyroidism should be exclude and family history should be reviewed. Patents with a positive family history for chronic pancreatitis can be offered genetic testing for hereditary pancreatitis.

European guidelines also recommend that in all patients with idiopathic CP, regardless of the time of presentation, a variant of cystic fibrosis should be excluded. If there are no pulmonary symptoms or male infertility, sweat electrophoresis is sufficient, otherwise testing for frequent CFTR mutations is recommended (14).

In patients with chronic pancreatitis unknown etiology despite this evaluation, autoimmune pancreatitis which represents up to 5% of cases should be excluded by additional investigations or a therapeutic trial (14). For the diagnosis of AIP we use international diagnostic guidelines based on a combination of imaging, serum IgG4, core needle pancreatic biopsy or major ampulla biopsy and response to corticosteroid therapy.

THERAPY

Acute exacerbations

Therapy of acute exacerbations of chronic pancreatitis does not differ from the treatment of acute pancreatitis.

Chronic pain

Chronic pain is the dominant symptom of chronic pancreatitis. They are present in most patients and significantly reduce the quality of life. The line of pain therapy of pain are **analgesic medications**. A standard escalation of therapy is recommended; paracetamol should be used as a first-grade analgesic, NSAIDs are effective but they have frequent gastrointestinal side effects. Tramadol is a second-degree analgesic. Third grade analgesics include strong opioids, for which oral use is recommended. If opioids are not effective, they should be stopped. Up to 5% of opioid users develop 'narcotic bowel syndrome' in which pain deteriorates with opioid dose. Pregabalin therapy is also recommended because of the neurogenic component of chronic pain. Antidepressants from the SSRI or TCA group can also be introduced.

Pancreatic exocrine insufficiency therapy with pancreatic enzymes (PERT) does not reduce pain.

Ending alcohol consumption slows down the progression of the disease and reduces pain. **Smoking** is associated with the rapid progression of disease, however there is no definitive evidence to link it to worsening pain. Most (90–95%) attempts to quit smoking are unsuccessful, and the guidelines therefore recommend support for smoking cessation with education, cognitive psychotherapy and drug therapy.

Endoscopic and surgical therapy can be successful in the treatment of chronic pain but do not slow the progression of pancreatic insufficiency. Pancreatic surgery with resection can even accelerate the onset of diabetes and pancreatic exocrine insufficiency. In randomized comparative studies, surgical pain therapy for patients with dilated pancreatic duct is on average, more effective than endoscopic therapy, with no detectable differences in mortality and morbidity. Despite this, most of the guidelines recommend endoscopic therapy as first line due to reduced invasiveness (14).

Endoscopic or surgical therapy should be considered when the chronic pain is not controlled by analgesics of the first and second degrees. Interventions are more effective at an early stage of the disease.

Endoscopic therapy is effective only in obstructive pancreatic pain with dilated pancreatic water (> 5mm), with duct strictures and / or pancreatic intraductal stones. In endoscopic therapy, the goal is decompression of obstructed duct. Most guidelines recommend endoscopic therapy as first-line therapy after unsuccessful drug therapy or necessity of opioid use. Endoscopic therapy is not indicated in asymptomatic disease, except in the case of biliary obstruction or pseudocysts with a high likelihood of complications.

Endoscopic extraction of stones with a basket with ERCP is unsuccessful in 80% for stones greater than 5mm, therefore extracorporeal should wave lithotripsy (ESWL) is recommended with subsequent removal of fragments in the ERCP. The procedure is effective for complete or partial improvement of pain in 70–96% of patients. ESWL with no subsequent ERCP is also effective.

With strictures of the main pancreatic duct (stricture with proximal dilation > 6mm and poor outflow of contrast in ERCP), endoscopic dilatations and short-term stenting are not effective in the long run. Long-term stenting (at least 1 year with at least one regular replacement) results in an eduring improvement in pain even after the removal of the stent in 2/3 patients. Very good results are also seen for insertion of multiple parallel plastic stents for 7 months, with long-term improvement of pain in 84% of patients - this therapy is recommended after unsuccessful long-term stenting with a single stent. After an endoscopic procedure an evaluation of the efficacy of therapy is required in 6–8 weeks. If unsuccessful, the patient must be evaluated by a multidisciplinary team (endoscopist, surgeon, radiologist) to examine the surgical options of therapy.

In patients with an inflammatory tumour of the head of the pancreas (head diameter > 4cm) and pain, the resection of the pancreatic head with drainage of the main pancreatic duct is indicated with or without the preservation of the duodenum. The purpose of the operation is to reduce pain and pressure on surrounding structures.

In patients with chronic uncontrolled pain without increased pancreatic head and with a dilated pancreatic duct, a drainage operation is indicated.

In patients with chronic uncontrolled without increased pancreatic head and without a dilated pancreatic duct or in patients with poor response to prior endoscopic or operative therapy, a total pancreatectomy is possible, possibly with the autotransplantation of B-Langerhans islets.

Biliary obstruction

Endoscopic therapy for biliary obstruction with multiple parallel plastic stents or fully covered self-expanding metal stents is successful in 90%. The patient must be relied upon to adhere to regular changes of the stents with ERPC, otherwise septic complications may occur. In non-compliant patients and in patients with an inflammatory tumour of the pancreatic head, surgery is recommended.

Pseudocyst

Pseudocysts are present in the course of chronic pancreatitis in 20–40% of patients. Up to 40% of pseudocysts that develop after an acute flare spontaneously resolve. A spontaneous resolution is rare after 12 weeks. Complications that require intervention develop in 2/3 cases. Pseudocysts larger than 5cm are associated with complications - pain, obstruction, infection or bleeding. Interventions may be endoscopic, surgical or radiological with similar efficacy but greater morbidity for surgical and radiological intervention therapy. The guidelines recommend the endoscopic drainage of symptomatic pseudocysts as the first method of

choice. Endoscopic therapy of asymptomatic chronic cysts > 5 cm can be performed because of the great potential of complications. Percutaneous drainage of chronic pseudocysts is not recommended because of the possibility of pancreatic-fistula formation.

Malnutrition

Malnutrition is common in chronic pancreatitis due to pancreatic exocrine and endocrine insufficiency, chronic pain and nausea in combination with frequent excessive alcohol consumption and smoking.

Regular monitoring of nutritional status is recommended (eg NRS -2002) and, if necessary, the determination of levels in the fat-soluble vitamins (A, D, E, K), Zn, Mg, and glycated haemoglobin. Patients with malnutrition should begin oral replacement of pancreatic enzymes (PERT) and dietetic counselling. Low-fat diets are not recommended, except in the case of unmanaged steatorrhea. Most patients threated dietary counselling and PERT do not need additional oral nutritional supplements.

Patients with chronic pancreatitis have a high risk of osteoporosis and pathological fractures, therefore regular measurement of bone density and vitamin D levels is recommended (14).

Diabetes

Annual monitoring of Hb1Ac and fasting glucose is recommended. DM type 3c is hard to manage and is associated with frequent hypoglycaemias. In case of mild hyperglycaemia and abstinence from alcohol, metforminim therapy may be initiated, other oral anti-diabetes drugs are not recommended. In most cases, insulin therapy is required.

Cancer

The diagnosis of early pancreatic cancer in the setting of chronic pancreatitis is very difficult, that is why there are no recommendations for screening. Screening with serum Ca 19-9 levels is not recommended. In hereditary pancreatitis the risk is greatest so monitoring of Ca 19-9 and annual EUZ can be performed. A preventative total pancreatectomy is an option.

Therapy of autoimmune pancreatitis (AIH)

Clinical response to systemic corticosteroids is one of the main features of AIP, so treatment efficacy is very high (99% for subtype I and 92% for subtype 2). Treatment should be started with methylprednisolone at a dose of 30–40 mg daily, 0.6 mg per kg body weight. After the 4th week of treatment, we begin a stepwise reduction in the dose of corticosteroid up to complete cessation.

Treatment lasts up to 12 weeks. Rituximab may be used in when steroids are contraindicated. After two to three weeks of treatment, there is a clinical improvement and regression of morphological changes in the pancreas. The endocrine and exocrine function of the pancreas also improve. Normalization of serum IgG4 occurs only after several months. The effect of treatment is monitored by imaging, usually CT. In the case of suspicion of pancreatic cancer, an imaging evaluation is required 2 weeks after initiation of therapy. One third of patients with AIH will have a recurrence of illness in 1-3 years, especially in type I. Patients with AIH type I with high activity of the disease can be offered maintenance treatment – low-dose of corticosteroid, azathioprine or rituximab are used.

PROGNOSIS

Yearly mortality is increased 3–4x compared to the population without chronic pancreatitis, with 70% survival after 10 years and 45% survival after 20 years. Continuing alcohol consumption is associated with poorer survival. In 20% of patients, death is due to a complication of acute exacerbation. In others death is due to malnutrition or other smoking related illnesses.

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PANCREATIC DISEASES

Textbook of Selected Topics in Clinical Gastroenterology

HEREDITARY AND AUTOIMMUNE PANCREATITIS

Lojze Šmid*, Jan Drnovšek**
University Medical Centre Ljubljana, Slovenia, Clinical Department of Gastroenterology

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ABSTRACT
Acute pancreatitis (AP) is one of the most common diseases of the gastrointestinal tract, leading to emotional, physical, and financial human burden. The incidence is estimated 50 cases per 100.000 worldwide. Patients with AP typically present with epigastric or left upper quadrant pain, combined with elevated pancreatic laboratory tests. The etiology of AP can be readily established in most patients. The most common cause of AP are gallstones (40–70 %) and alcohol abuse (25–35%). Other, but rare causes of AP are metabolic causes (hypercalcemia, hyperlipidemia), infectious agents, medications, and morphological features of pancreas and pancreatic injury due to iatrogenic causes. Hereditary pancreatitis (HP) and autoimmune pancreatitis (AIP) are rare causes of acute pancreatitis. HP is an autosomal dominant genetic condition, where mutations increase autocatalytic conversion of trypsinogen to active trypsin, while it is still in the pancreas, which leads to inflammation. Autoimmune pancreatitis (AIP) is the pancreatic manifestation of a systemic fibroinflammatory disorder due to lymphocyte infiltration and fibrosis.

Key words: *chronic pancreatitis, hereditary pancreatitis, autoimmune pancreatitis, pancreatic cancer*

HEREDITARY PANCREATITIS

Introduction

Hereditary pancreatitis (HP) is a rare cause of chronic pancreatitis and occurs with an autosomal dominant pattern of inheritance with high (80%) penetrance (1). It has to be differentiated form familial pancreatitis, which refers to chronic pancreatitis that occurs in patients with at least one relative, regardless of the etiology (2). European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) defines pancreatitis as hereditary if it has no precipitating factors and occurs in two or more first-degree relatives or three or more second-degree relatives in two or more generations (3). All patients with chronic pancreatitis have increased risk for developing pancreatic cancer. HP carries the highest risk of all etiologies, as pancreatic carcinoma occurs in four out of ten HP patients (4).

Pathogenesis

Precursors to pancreatic digestive enzymes are stored in zymogen granules in pancreatic acinar cells. The activation of zymogenes (e.g. cationic and anionic trypsinogen) is tightly controlled and normally occurs in the duodenal lumen by proteolytic action of enterokinase. Premature activation of digestive enzymes in the pancreas is the major cause of pancreatic injury and immune system activation, leading to acute pancreatitis and later chronic pancreatitis. The primary defense against pancreatitis is to control trypsin activity, either through prevention of premature activation of trypsinogen to trypsin, or by the destruction, inhibition, or elimination of trypsin from the pancreas. These defenses are weakened by mutations in the serine protease 1 gene, which encodes cationic trypsinogen (PRSS1), or in genes coding for molecules that protect the pancreas from active trypsin (SPINK1, CFTR) (5).

* Lojze Šmid, MD, PhD
University Medical Centre Ljubljana, Slovenia, Clinical Department of Gastroenterology, Japljeva 2, SI–1000 Ljubljana.
** Jan Drnovšek, MD
University Medical Centre Ljubljana, Slovenia, Clinical Department of Gastroenterology, Japljeva 2, SI–1000 Ljubljana.

Cationic trypsinogen - PRSS1.

Mutations in the serine protease 1 gene (PRSS1), which encodes cationic trypsinogen, are the most frequent cause of HP. The most common mutation in PRSS1 is the p.R122H at the autolysis site (6), which renders trypsin resistant to autoproteolysis, thus interfering with important mechanism that protects from premature trypsin activation (7). The second most common mutation N21I causes misfolding of trypsin and lowers its binding affinity for protease inhibitor SPINK1 (8). Other mutations, associated with HP are much less frequent (A16V, D22G in K23R) (9).

Serine protease in hibitor Kazal type 1 - SPINK1.

Chronic pancreatitis is also associated with N34S mutation in SPINK1 (10). SPINK1 mutations can cause familial pancreatitis with an autosomal recessive pattern in families (11). However, the majority of patients with SPINK1 mutations and chronic pancreatitis are heterozygous. N34S mutation has been described in 43 % of patients with early-onset chronic pancreatitis (12). This mutation is also frequently found in patinets with chronic alcoholic (13) and tropical (14) pancreatitis and probably acts as a disease modifier, lowering the threshold for developing pancreatitis from other genetic or environmental factors.

Cystic fibrosis transmembrane conductance regulator gene – CFTR.

Mutations in the CFTR can cause pancreatitis with or without associated manifestations of cystic fibrosis (15, 16) and are also found in up to one third of patients with chronic pancreatitis of other etiologies (10, 11).

Environmental influences.

The occurrence of HP is higher in two separate age groups with the first peak around age 8 and the second between ages 18 and 24. The onset of HP in early adulthood coincides with the onset of alcohol consumption (17, 18). Cigarette smoking also appears to be more prevalent in HP patients compared to healthy controls (18). The roles of ethanol consumption and cigarette smoking in the development of HP have not been statistically verified, but are in accordance with known effect of smoking on the course of idiopathic or alcoholic chronic pancreatitis (19, 20).

Clinical presentation

The onset of HP is characterized by recurrent episodes of acute pancreatitis in childhood or early adulthood (21). Acute episodes are indistinguishable from acute pancreatitis of other causes. The most common clinical presentation is sudden recurrent upper abdominal pain (22) with two to four recurrences per year. Complications are rare and include formation of necrosis, thrombosis of splenic vein (23), pseudocyst formation (24) or death (25). Chronic pancreatitis develops after several acute episodes and is indistinguishable from idiopathic juvenile chronic pancreatitis in children or chronic alcoholic pancreatitis in adults (26, 27). EUROPAC study estimated cumulative risk for the development of exocrine pancreatic insufficiency in patients with HP to 8.4% at the age of 20 years and 60.2% at 70 years. Endocrine insufficiency with diabetes develops in 4.4% of patients at 20 years and 47.6% at the age of 50 years (3). HP appears to be associated with 1–2% of all cases of acute pancreatitis (28–30).

Genetic testing

Genetic testing has become widely available in everyday clinical practice. Current IAP guidelines recommend the use of genetic testing only in symptomatic patients with idiopathic or recurrent pancreatitis and at least one close relative with similar condition, who are adequately informed and consent to testing (26). Children can be tested during their first episode of etiologically unexplained acute pancreatitis. Genetic testing is also recommended in children with recurrent abdominal pain and positive family history. Positive results of genetic testing should be explained to patients with clear emphasis of variability and unpredictability of HP clinical course. Clear strategies for preventive measures and early detection and treatment of pancreatic cancer have to be communicated to HP patients.

Pancreatic cancer in HP patients

Patients with chronic pancreatitis from any cause are 3,8 to 16,5 times more likely to develop pancreatic cancer than healthy individuals. The risk of pancreatic cancer is significantly higher in patients with hereditary pancreatitis with a lifetime risk of 40% (4).

IAP therefore recommends risk reduction and early detection strategies (27). The frequency of acute episodes is linked to risk of chronic pancreatitis and pa-

tients with HP therefore have to be counseled regarding the risk of smoking and alcohol use. All patients with hereditary pancreatitis should undergo regular imaging (endoscopic ultrasound - EUS and magnetic resonance cholagiopancreatography - MRCP) after reaching the age of 40 (28). The roles of prophylactic pancreatectomy or pancreatectomy with islet autotransplantation as cancer preventing strategy have not yet been prospectively evaluated.

AUTOIMMUNE PANCREATITIS

Introduction

Autoimmune pancreatitis (AIP) is an infrequently recognized disorder of autoimmune etiology that is associated with characteristic clinical, histologic, and morphologic findings (31–34).

AIP frequently occurs in association with other disorders of presumed autoimmune etiology, histologically characterized by lymphoplasmocytic infiltration and fibrosis, including IgG4 cholangitis, salivary gland disorders, mediastinal fibrosis and retroperitoneal fibrosis and tubulointerstitial disease (35–37). AIP accounts for 4–6% of all cases of acute pancreatitis according to Japanese, Korean and Italian data. Estimated incidence rate of AIP in Japan is 0.82 cases per 100.000 persons per year (38–41). AIP is twice more common in females than males and usually occurs in the sixth and seventh decade (42–44).

Types of autoimmune pancreatitis

AIP is classified into two types (1 and 2). In type 1 AIP (lymphoplasmacytic sclerosing pancreatitis), the pancreas is involved as one part of a systemic IgG4-positive disease. Characteristic histologic findings in inflamed gland tissue are IgG4-positive cells with periductal lymphoplasmacytic infiltrate, obliterative phlebitis and acinar fibrosis. Type 2 AIP (idiopathic duct centric pancreatitis) is characterized by histologically confirmed idiopathic duct centric pancreatitis often with granulocytic lesions, but without IgG4-positive cells and without systemic involvement (45–49).

Type 1 AIP is more frequent and diagnostic algorithms are focused towards recognition of type 1 AIP. The diagnosis of type 2 AIP can be established histologically. Fine needle aspiration biopsy is insufficient for AIP diagnosis (50). The two types of AIP differ in epidemiology, serology, disease course and response to treatment. However, clear distinction between the two types can sometimes be difficult due to overlapping diagnostic criteria (51).

Clinical presentation

Billiary obstruction, accompanied by pancreatic mass, is the most common clinical manifestation of AIP and can be confused with pancreatic malignancy. It is frequently accompanied by (often mild) abdomnial pain and elevation of pancreatic enzymes. AIP is a rare cause of recurrent acute and chrnic pancreatitis, which can lead to exocrine and endocrine pancreatic insufficiency. A number of other organs can be involved in patients with AIP. These include the salivary glands (Sjögren's syndrome), bile duct strictures, lung nodules, autoimmune thyroiditis, and kidney (interstitial nephritis with an IgG4-positive plasma cell infiltrate and IgG4 deposits in the tubular basement membrane) (52–54).

Imaging

Transabdominal ultrasound examination is routinely performed in patients with cholestasis and abdominal pain. Hypoechoic pancreatic parenchyma and dilatation of main pancreatic duct can sometimes be visualized. Computed tomography (CT) and MR have higher sensitivity. Main findings that are diagnostic or highly suggestive of AIP are a diffusely enlarged pancreas with featureless borders and delayed enhancement with or without a capsule-like rim. EUS guided biopsies are used for differentiation of AIP from pancreatic cancer (55–57).

Serology

Serologic testing for IgG4 is an important component of evaluating a patient suspected of having autoimmune pancreatitis. A serum concentration of IgG4 that is twice the upper limit of normal (serum IgG4 $\leq$ 280 mg/dL) is highly suggestive of AIP. However, it should be noted that up to 10% of pancreatic cancer patients exhibit higher IgG4 concentrations and serology can thus not be used as a test for exclusion of pancreatic cancer (59).

Diagnostic criteria

Diagnostic criteria have been proposed by several groups including the Japanese Pancreas Society, an expert group from Korea, and the Mayo Clinic in the

United States (55, 60). The diagnostic criteria proposed by the Mayo Clinic (the "HISORt" criteria) are most commonly used and include the presence of diagnostic histology (H), characteristic imaging on computed tomography and/or pancreatography (I), elevated serum IgG4 levels on serologic testing (S), other organ involvement (O) and response of pancreatic and extrapancreatic manifestations to glucocorticoid therapy (Rt).

Treatment

Most patients with AIP respond to glucocorticoid therapy, but the relapse rate is significant. Glucocorticoids (methylprednisolone 0.6 mg / kg, up to 12 weeks) improve clinical manifestations and prevent complications. In most reports, one-half to two-thirds of patients responded to glucocorticoids, but about 25 percent required a second course of treatment, while a smaller proportion needed continuous treatment. Azathioprine can be used in relapsing patients.

The time to response is variable, usually occurring within two weeks to four months. Patients are typically followed with serum IgG4 levels, liver biochemical tests, and by CT scan while on therapy.

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PANCREATIC DISEASES

Textbook of Selected Topics in Clinical Gastroenterology

NEW ALGORITHMS IN DIAGNOSING BILIOPANCREATIC PATHOLOGY WITH ENDOSCOPIC ULTRASOUND

Rusmir Mesihovic*
Medical faculty University Sarajevo, Bosnia and Herzegovina and Medical Center Barsos Ljubljana, Slovenia

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ABSTRACT
Endoscopic ultrasound (EUS) continues to present a rich source of innovation, allowing it to evolve from a diagnostic procedure to a therapeutic modality. EUS is one of the most important modalities for the diagnosis of biliopancreatic pathology. This review is the principle, indications, main literature results, limitations and future expectations for each of the methods presented. Endoscopic ultrasound is a very accurate imaging technique with a relevant clinical impact in the diagnosis and staging of various conditions such as pancreatic-biliary lesions. New technologies in EUS evaluation have been developed because of the need to improve the EUS and EUS-fine needle aspiration (EUS-FNA) diagnostic rate. Several techniques of image enhancement have been developed in recent years in the attempt to make the technique less operator-dependent. Among them the most important appear to be contrast harmonic-endoscopic ultrasound and endoscopic ultrasound-elastography. Both techniques show promising applications in the study of pancreatic tumors including differential diagnosis and providing guidance to fine needle aspiration. It is also useful for the discrimination of pancreatic masses based on their qualitative patterns. Needle confocal laser endomicroscopy offers useful information about cystic lesions of the pancreas and is still under evaluation for use with solid pancreatic lesions of lymph nodes.

Key words: *Endoscopic ultrasound, fine-needle aspiration, contrast-enhanced, elastography, endomicroscopy, endosonography-fine needle aspiration*

* Professor Rusmir Mesihovic, MD, PhD.
Medical Faculty University Sarajevo, Bosnia and Herzegovina and Medical Center Barsos Ljubljana, Slovenia.

PANCREATIC DISEASES

Textbook of Selected Topics in Clinical Gastroenterology

RISK FACTORS FOR DEVELOPMENT OF PANCREATIC DUCTAL ADENOCARCINOMA

Sanjo Finderle*, Borut Štabuc**
University Medical Centre Ljubljana, Slovenia, Clinical Department of Gastroenterology

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ABSTRACT
Pancreatic ductal adenocarcinoma is highly fatal and has a poor prognosis. The reasons for low survival are low rates of curative resection due to local infiltration and distant metastases. Risk factors can be non-modifiable (age, familial cancer syndromes, race, hereditary and other forms of chronic pancreatitis, blood group, diabetes mellitus) and modifiable (obesity, smoking, diet, alcohol intake).

Key words: *pancreatic cancer, risk factors, smoking, chronic pancreatitis, familial cancer syndromes*

INTRODUCTION

The pancreas gives rise to several malignant and benign neoplasms. The commonly used term "pancreatic cancer" usually refers to a ductal adenocarcinoma of the pancreas (including its subtypes), which represents about 85% of all pancreatic neoplasms. Ductal adenocarcinoma may vary from well differentiated to poorly differentiated, the most common being moderately differentiated cancer (1).

The incidence of pancreatic cancer has been rising in the last two decades (2). It is the eighth most common cancer in Europe (3). Thus, in men and women, it is ranked fourth in terms of mortality among all cancers (4). According to the Cancer Registry of Republic of Slovenia there were 350 new cases of pancreatic cancer in Slovenia (183 men and 167 women) in 2013. 356 patients (175 men and 181 women) died. Five-year survival rate is only 5% (5).

Most cancers are diagnosed in an advanced stage when the disease is already unresectable, so the median survival is from 3 to 11 months (6, 7). The median survival of patients with resectable cancer is from 13 to 24 months, depending on the stage, but fewer than 10% of tumors are detected early enough (6, 8, 9).

Studies have identified certain risk factors which may predict increased odds of developing pancreatic cancer.

RISK FACTORS FOR PANCREATIC CANCER

Risk factors can be divided as either non-modifiable (host) and modifiable risk factors (enviromental).

Host factors

Age

Pancreatic cancer is rare in the first three decades of life. After the age of 30, the incidence begins to increase exponentially, reaching its peak in the 7th and 8th decade (10). Patients who are diagnosed with an early disease stage, are on average 2.3 years younger than those with advanced disease. This suggests that the time of progression from early to advanced stage in about 1–2 years (11).

* Sanjo Finderle, MD
University Medical Centre Ljubljana, Slovenia, Clinical Department of Gastroenterology, Japljeva 2, SI–1000 Ljubljana.
** Professor Borut Štabuc, MD, PhD
University Medical Centre Ljubljana, Slovenia, Clinical Department of Gastroenterology, Japljeva 2, SI–1000 Ljubljana.

Sex

Pancreatic cancer occurs more frequently in males than in females (1.3:1 ratio). Several studies on hormone-related risk factors have been (12, 13). A recent meta-analysis concluded that reproductive hormones are not associated with a greater risk of developing pancreatic cancer in women. This suggests that the difference between males and females could be attributed to environmental factors. Nevertheless, we certainly do not yet know all of the genetic factors affecting incidence and mortality in men and women (12).

Race

Race is a known risk factor for the development of pancreatic cancer. In the United States, the incidence of pancreatic cancer is higher in African-Americans than in Caucasians (14.8/100.000 in African Americans compared to 8.8/100.000 in the general population) (9). In the past, higher incidence was attributed to dieting, alcohol consumption, smoking and vitamin D deficiency. Recent epidemiological studies suggest that other factors are likely to contribute to increased risk in African Americans (14). These factors include race specific genetic differences that contribute to a higher risk of mutations due to exposure to known toxins (e.g. the ability to detoxify products from tobacco use) (15, 16).

Blood type

Large epidemiological studies have shown that there is a link between ABO blood groups and the risk of developing pancreatic cancer. People with blood type A, AB, and B have a greater risk of developing this type of cancer than those with O blood type (the ORs for groups A, AB, and B are 1.38 (95% CI: 1.18-1.62), 1.47 (95% CI: 1.07-2.02) and 1.53 (95% CI: 1.21-1.92)). These findings are also supported by the results of a genomic study that identified variants in the ABO locus (9q34), which is associated with a higher risk of developing pancreatic cancer (17). The pathogenetic mechanism behind this link is not yet known.

Genetic factors

Pancreatic cancer is essentially a genetic disease caused by inherited and acquired mutations. Genetic variations/mutations play an important role in both familial and non-familial (sporadic) cancers. More than 80% of pancreatic cancer develops due to sporadic mutations. A small proportion develops due to inherited germline mutations.

1) Inherited Genetic mutations (Germline Mutations)

Mutations in germline are associated with a higher risk of developing pancreatic cancer in certain genetic syndromes and in certain familial pancreatic cancer kindreds (see Table 1).

➔Familial Pancreatic Cancer:

Familial Pancreatic Cancer is defined as the occurrence of pancreatic cancer in at least two first-degree relatives with pancreatic cancer. The risk of pancreatic cancer increases exponentially. When two first-degree relatives have pancreatic cancer, the risk is increased 18 fold. When three first-degree relatives have pancreatic cancer, the risk is 57-times higher (18). BRCA2 mutation is the most common inherited mutation, other mutations, such as PALB2, have also been reported.

➔Family cancer syndromes:

An increased risk of developing pancreatic cancer is found in many inherited cancer syndromes. These include Familial Dysplastic Neuromuscular Syndrome, hereditary pancreatitis, Peutz-Jeghers syndrome, cystic fibrosis, hereditary breast and ovarian cancer, Fanconi anemia, familial adenomatous polyposis, Li-Fraumeni syndrome and Lynch syndrome. These syndromes are associated with germline mutations in certain genes such as BRCA2, p16, ATM, STK11, PRSS1, SPINK1 and PALB2 (see Table 1).

2) Acquired genetic mutations (Somatic Mutations)

➔Genetic risk in Non-Familial Pancreatic cancer:

The mutations in somatic cells may also lead to the development of pancreatic cancer. The development is associated with mutations in four main genes: K-ras (95% tumors), CDKN2A (p16) (90%), p53 (75%) and SMAD4 (55%) (19–21). The development and growth of cancer takes place through several steps including initiation, progression, invasion and ultimately the spread of the disease. Pancreatic cancer origi-

nates in the ductal epithelium and develops from a premalignant lesion to invasive cancer. The progression from minimally dysplastic epithelium (PanIN 1A and 1B) to severe dysplasia (PanIN 2 and 3), and finally to invasive carcinoma, is accompanied by accumulation of mutations. These include activation of Kras2 oncogenes, inactivation of the tumor suppressor gene CDKN2a/INK4a and finally inactivation of tumor suppressor genes TP53 and DPC4/SMAD4 (22). On average there are 63 genetic alterations, most of them are point mutations. The changes affect 12 major signalling pathways and processes. They are found in 67–100% of pancreatic cancers (23).

Chronic pancreatitis

Chronic pancreatitis is a progressive inflammatory disease of the pancreas. It consists of the destruction of acinar cells and pathological fibrosis. The most common etiologies are alcohol abuse, hereditary pancreatitis and idiopathic pancreatitis. Chronic pancreatitis is a risk factor for the development of pancreatic cancer. Ten-year cumulative risk is 1.8% and twenty-year risk is for 4%, regardless of the etiology of the pancreatitis (24)

The relationship between pancreatitis and pancreatic cancer is very important in otherwise rare autosomal dominant hereditary pancreatitis. The cancer risk is 70 times greater than in general population, and the lifetime risk is 40–55% (25). Increased risk is due to inflammation accompanied by somatic and hereditary mutations. Smoking further contributes to increased risk.

Diabetes mellitus

Diabetes mellitus is a risk factor for the development of pancreatic cancer, but it may also be its manifestation. A meta-analysis of 88 studies (50 cohort studies and 30 case studies with controls) showed a higher relative risk of pancreatic cancer in diabetic patients compared to patients without diabetes (RR 2.08; 95% CI: 1.87-2.32) (26). The longer the patient has diabetes, the greater the risk (27). Patients with newly detected pancreatic cancer have a greater risk of developing diabetes, especially within three years of diagnosis (28).

Studies also suggest that hyperglycaemia, exposure to higher insulin levels and insulin resistance are associated with the higher risk of development of pancreatic cancer (29).

Anti-diabetic drugs and risk of pancreatic cancer

Basic and epidemiological studies suggest that insulin may increase the risk of developing pancreatic cancer. Insulin increases the use of glucose and proliferation of cancer cells by activating MAP kinases and PI3 kinases. It also increases the expression of the GLUT-1 receptor (30). Patients treated with insulin have a higher risk of developing pancreatic cancer (OR 3.54; 95% CI: 2.27-6.16) than patients treated with oral antidiabetic drugs (OR 1.53; 95% CI: 1.06-2.23) (31). In contrast, patients who receive metformin might have reduced incidence of pancreatic cancer (OR 0.38; 95% CI: 0.22-0.69) (32).

Pancreatic cysts

Pancreatic cysts are present in 15–20% of the population. Patients with mucinous cystic neoplasms and intra-ductal papillary mucinous neoplasms of the pancreas (IPMN) have a greater risk of developing pancreatic cancer. The median risk of developing pancreatic cancer in the main duct IPMN is 61.6%. The median risk for the branch duct IPMN is 25.5% (33). If IPMN develops into invasive cancer, it is usually referred to as IPMN associated with adenocarcinoma. Patients with IPMN are also at risk of developing pancreatic cancer, which occurs at a different location than cysts. Pancreatic cancer occurs in 2-9% of patients who are monitored for IPMN (34).

Factors related to lifestyle

Obesity and physical activity

Obesity (defined as Body Mass Index (BMI) ≥30 kg/m^2) and elevated BMI are both risk factors for developing pancreatic cancer. A recent meta-analysis showed that obese men and women had a higher risk than normal body weight individuals (Men: RR 1.36; 95% CI: 1.07-1.73; Women: RR 1.34; 95% CI: 1.22-1.46). Moderate physical activity has a beneficial effect on the risk of developing pancreatic cancer, especially in those with BMI ≥25 kg/m2 (RR 0.45; 95% CI: 0.29-0.70) (35).

There are several suggested pathogenetic mechanisms for increased risk of pancreatic cancer with higher weight. Obesity may be associated with physical inac-

tivity and unhealthy diet and lifestyle. Undetected genetic factors may also play a role in increasing the risk. At the cellular level, adipocytes may release potential procarcinogenic mediators such as adipokines, IGF and VEGF. These mediators cause chronic inflammation, which may play a role in the development of pancreatic cancer (36).

Diet

Studies evaluating the relationship between diet and pancreatic cancer are inconclusive:

➔Diets with high content of saturated fatty acids and/or meat, especially smoked or processed, have been associated with an increased risk of development of pancreatic cancer in several (15, 37–39) but not all (40–42) studies .

➔Several (43–45) case-control studies report a protective effect from the consumption of fresh fruits and vegetables, but prospective studies have not observed such association (46).

➔The role of 25-hydroxyvitamin D has also been studied. Higher levels were associated with a 35% reduction in the risk of pancreatic cancer (47).

Alcohol

Alcohol has long been suspected of being a risk factor for the development of pancreatic cancer, because of its role in the etiology of chronic pancreatitis. Alcohol has various effects on the exocrine and endocrine function of the pancreas. It is believed that ethanol metabolism affects intracellular redox status, which could play a major role in the development of chronic pancreatitis and pancreatic cancer (48).The metabolism of ethanol through oxidation with alcohol dehydrogenase or through the microsomal oxidation system generates toxic metabolites such as acetaldehyde and reactive oxygen species. These metabolites activate pancreatic stellate cells, which leads to fibrosis and the release of inflammatory mediators (cytokines, NF-kB, COX-2). Consequently, genetic alteration and damage to cells may occur, which contribute to carcinogenesis.

A meta-analysis of 19 prospective studies has shown that low or moderate alcohol consumption had negligible or low effect on the development of pancreatic cancer. High alcohol consumption was associated with an increased risk of pancreatic cancer (RR 1.15; 95% CI: 1.06-1.25). The risk was highest for those who consumed spirits (RR 1.43; 95% CI: 1.17-174) (49). The effect of alcohol consumption on pancreatic cancer is usually difficult to assess due to ’due to existence of counfouders (e.g. smoking).

Smoking

Tobacco smoking is the most important environmental factor for the development of pancreatic cancer. Smokers have a 25–35% higher risk (50). The pancreas, unlike the lungs, is not directly exposed to tobacco. Carcinogens reach it through the blood stream or possibly via the bile or duodenum content, as most pancreatic cancers occur in the head (51). A meta-analysis of 30 cohort studies has shown that smokers have a 60% higher risk of developing cancer than those who have never smoked (HR 1.61; 95% CI: 1.12-2.32). After cessation, the risk decreases slowly and after 20 years it comes to baseline (18). Passive smoking is also associated with an increased risk of developing cancer. A European prospective cohort study has shown that in those who have been exposed to smoking the risk is doubled (52). Smoking also greatly increases the risk in people having other risk factors. Patients with hereditary pancreatitis who smoke have a two-fold higher risk of developing pancreatic cancer, which occurs at a significantly lower age (53).

Helicobacter pylori infection

Studies also suggest the association of pancreatic cancer with H. pylori infection. A meta-analysis involving 1083 patients with pancreatic cancer and 1950 controls showed increased risk for those who were infected with H. pylori (OR 1.47; 95% CI 1.2-1.8) (54). Further research will be needed to clarify this link better.

PROTECTIVE FACTORS

Statins

Statins are medicines for lowering lipids that are primarily used in the treatment of hyperlipidemia. They were also associated with other beneficial effects, such as reduced risk of developing cancer. Risk reduction is probably due to pleotropic effects (changes in growth signaling pathways, immunomodulatory and anti-inflammatory effects). Some studies suggest that the use of statins contributes to a lower risk of developing pancreatic cancer and even contributes to a better survival of patients with pancreatic cancer (55, 56).

Acetylsalicylic acid and non-steroidal anti-

inflammatory drugs

Data from laboratory and animal studies indicate that regular use of these medicines could inhibit pancreatic carcinogenesis. Epidemiological studies in humans showed contradictory results (57, 58).

Allergies

Epidemiological studies show that patients with allergies have a lower risk of developing pancreatic cancer. Respiratory allergies (without asthma) reduce the risk by 37% and skin allergies by 34% (59).

CONCLUSION

Pancreatic cancer related mortality is not decreasing. This is attributed to the late detection of the disease and the lack of effective therapies. Several factors also affect the risk of this disease. The most important risk factors are cigarette smoking, high body mass and lack of physical activity, nonhereditary chronic pancreatitis, hereditary risk factors (e.g. hereditary pancreatitis), other highly penetrant conditions caused by germline mutations in known cancer-causing genes and familial pancreatic cancer, and pancreatic cysts. It is important to identify patients at higher risk and provide them with appropriate advice on the factors that can be influenced.

Group (mutated gene)	Other characteristics	Relative risk for pancreatic cancer	Lifetime risk for pancreatic cancer by age 70 years (incidence)
No history		1	0.5%
HBOC (BRCA1)	Predisposition to breast, ovarian, prostate cancer	3	1.2%
HBOC (BRCA2)	Predisposition to breast, ovarian, prostate cancer, Jewish ancestry in some (refer for gene testing)	3.5–10	2–5%
HBOC (PALB2)		unknown	unknown
Peutz-Jeghers syndrome (STK11)		132	11–66%
FAMMM (CKDN2A)	Predisposition to melanoma, multiple nevi, atypical moles (autosomal dominant)	13–36	10–19%
Lynch II syndrome (mismatch repair genes MLH1, MSH2, MSH6)	Predisposition to colorectal, endometrial cancer	8.6	3.7%
Li-Fraumeni (TP53)		unknown	unknown
Familial PC + 1 FDR affected	Pancreatic ductal adenocarcinoma in an individual with one affected FDR (sibling, parent, or child)	4.6	
Familial PC+ 2 FDR affected (unknown)	Pancreatic ductal adenocarcinoma in an individual with two affected FDRs	6.4	
Familial PC + 3 FDR affected (unknown)	Pancreatic ductal adenocarcinoma in an individual with three affected FDRs	32	
Hereditary pancreatitis (PRSS1, SPINK1)	Young-onset pancreatitis (autosomal dominant)	50–82	25–44%

Table 1: *Pancreatic cancer predisposition syndromes and risk of pancreatic cancer* (60).

Factor	Relative risk	Attributable fraction
Tobacco	2	11–32%
H. pylori infection	1.5	4–25%
Non-0-blood group	1.4	13–19%
Diabetes mellitus	1.4–2.2	1–16%
Obesity	1.2–1.5	3–16%
Red meat intake	1.1–1.5	2–9%
Heavy alcohol intake	1.1–1.5	9%
Low fruit and folate intake	0.5–1.0	<12%

Table 2: *Major non-genetic risk factors* (61).

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PANCREATIC DISEASES

Textbook of Selected Topics in Clinical Gastroenterology

ENDOSCOPIC PROCEDURES IN PATIENT WITH PANCREATIC DISEASE

Samo Plut*
University Medical Centre Ljubljana, Slovenia, Clinical Department of Gastroenterology

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ABSTRACT
Endoscopy has an important role in diagnosis and treatment of diseases of the pancreas. Endoscopic retrograde cholangiopancreatography (ERCP) used to be the main diagnostic modality; however in modern times it is almost always preceded by less invasive modern imaging techniques as is computer tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS). ERCP still has an important role as a therapeutic tool in treatment after diagnosis was made. Development of interventional EUS enables us better and safer diagnostic and treatment options. Both endoscopic diagnostic methods have become standard of care of modern management of patients with such pathology.

Key words: *ERCP, EUS, diseases of pancreas, diagnostic, treatment*

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) has been used in the diagnosis and treatment of pancreatic and biliary disease for more than 40 years. The procedure is performed with a duodenoscope, which enables optimum display of papillae Vateri and minor papillae due to lateral optics. The presence of the elevator channel facilitates cannulation of papilla and introduction of guiding wire into biliary and pancreatic duct as well as injecting a contrast agent. ERCP is associated with a significant risk of developing iatrogenic pancreatitis (in 5-10% of cases), major complications include bleeding and perforation after endoscopic sphincterotomy or balloon dilatation and post-ERCP cholangitis. Initially primarily diagnostic method evolved into almost exclusively therapeutic intervention procedure. Modern non-invasive imaging diagnostic methods, such as computed tomography (CT), magnetic resonance imaging (MR and MRCP), and endoscopic ultrasound (EUS) are the current diagnostic methods of choice. The learning curve for ERCP is long, which is especially true for diagnosis and therapy in the pancreatic ductal system. Achieving endoscopic competence requires an experienced endoscopist with a sufficient number of procedures done annually.

Endoscopic ultrasound (EUS) probe is located on the tip of an endoscope, which is introduced through the esophagus and stomach into the duodenum. This enables us to place the probe very close to the pancreas and high-resolution display of even the smallest structures and changes. Development of linear EUS enabled this primarily diagnostic method to evolve into a useful therapeutic method of fine needle aspiration (FNA) cytology and histology tissue sampling as well as placement of lumen opposing stent placement (LAMS).

* Samo Plut, MD
University Medical Centre Ljubljana, Slovenia, Clinical Department of Gastroenterology, Japljeva 2, SI–1000 Ljubljana.

Gastroscopy has a minor role in management of patients with pancreatic disease. By endoscopic placement of metal stents, digestive tract obstruction in patients with advanced pancreatic cancer is resolved.

ENDOSCOPY AND MALIGNANT DISEASE OF THE PANCREAS

Pancreatic cancer remains a disease with grave prognosis and difficult treatment. Clinically, the symptoms of the disease appear late in course. Successful curative treatment is possible only in the early stages of the disease. Lesions in the pancreas may be either solid or cystic.

Cystic pancreatic lesions are often a diagnostic and therapeutic challenge. Pseudocysts are benign lesions with no malignant potential. Mucinous cystic neoplasms and intraductal papillary mucinous neoplasms (IPMN) are premalignant lesions. Some malignant tumors can include areas of cystic degeneration (solid pseudopapillary tumor, cystic neuroendocrine tumor or even ductal adenocarcinoma). EUS plays a key role in management of cystic lesions, allows us identify a cystic lesion with possible solid inclusions, thickened cyst wall and provides a good assessment of pancreatic duct. Application of an intravenous contrast medium enhances diagnostic value of EUS even further. EUS FNA enables aspiration of cysts and thus cytological and biochemical evaluation (determination of CEA in cystic fluid), with high specificity (88–93%) and good sensitivity (54–63%). ERCP is rarely used in the diagnosis of cystic lesions, however a pathognomonic feature of main-branch IPMN can be seen endoscopically - draining of mucus form the papilla of Vater (fish-eye papilla). ERCP can provide a good imaging of the pancreatic ductal system, but is (due to the invasiveness of the procedure and potential complications) used only after of adjunct to MRCP. Histological and cytological diagnostics of IPMN at ERCP (cytological brushing and biopsy) have relatively low sensitivity (35%) and are rarely used.

ENDOSCOPY AND BENIGN DISEASE OF THE PANCREAS

The etiology of **acute pancreatitis** is biliary in about 40% cases. EUS has very good sensitivity (94%) and specificity (95%) for detecting cholelithiasis, which is comparable to MRCP in stones greater than 10 mm, while EUS is superior in smaller stones and biliary sludge. EUS can diagnose any possible anatomical abnormalities (pancreas divisum) or ampullary adenoma. Because the vast majority of biliary stones (up to 80%) passes the bile duct spontaneously, ERCP is indicated only in patients with acute biliary pancreatitis and persistent biliary obstruction or cholangitis, and in patients where non-invasive diagnostic methods (US, CT, MRI or EUS) diagnosed choledocholithiasis. ERCP should be done as soon as possible, and no later than 24-72 hours. A retrospective study of Slovenian patients (Dpt. of gastroenterology, UMC Ljubljana) showed that in patients' acute biliary pancreatitis (ABP) and early ERCP (preformed within 24 hours of pancreatitis onset) compared to postponed ERCP (later then 24h), local and systemic complications of pancreatitis as well as total hospital stay duration are reduced. ERCP enables us to perform endoscopic sphincterotomy and / or dilatation of the papilla Vateri and extraction of biliary stones. The role of endoscopic sphincterotomy in patients with ABP, where stones have already spontaneously passed, is not entirely clear. It is recommended in patients who are not candidates for cholecystectomy or it will not be made within 4 weeks. Common complication of severe acute pancreatitis is formation of pancreatic and peripancreatic fluid collections. Smaller uninfected collections may resolve spontaneously. The intervention is indicated in case of symptoms (abdominal pain, early satiety, gastric outlet obstruction, icterus or weight loss) and the case of larger collections or if the collection gets infected. Endoscopic intervention is a good alternative to surgery and is less invasive. It includes papillotomy of the pancreatic sphincter and insertion of a pancreatic stent (by ERCP) and endoscopic drainage of pseudocysts and limited fluid collections (by ERCP or EUS) - cystogastrostomy or duodenostomy. It provides an endoscopic approach to retroperitoneum and endoscopic necrosectomy.

Pancreas divisum is a congenital anomaly in the anatomy of pancreas with the absence of the dorsal and ventral pancreatic duct fusion in embryogenic development. It is present in about 7% of people and is associated with recurrent acute and chronic pancreatitis. EUS is the diagnostic method of choice with better sensitivity as MRI and CT. ERCP with cannulation of the minor papilla and contrast imaging is the best method, however due to technically difficult procedure and potential complications, it is indicated only

in patients with unclear non-invasive diagnostics and for therapeutic purposes – symptoms improve in 60% of patients after endoscopic sphincterotomy of minor papillary pancreatic sphincter.

Oddi sphincter dysfunction (SOD) is considered to be a functional pancreatic disease. Up to 72% of idiopathic recurrent pancreatitis are presumably caused by SOD. By EUS we can accurately assess the pancreatic duct and exclusion of other potential pathology. According to the Milwaukee classification, SOD is classified in three types. ERCP with sphincterotomy is indicated for type 1 (patients with typical pain, elevated pancreatic enzymes and dilated pancreatic duct). In the patients with type 2 and 3, the Oddi sphincter manometry could have a diagnostic role, however it is rarely available and not performed in Slovenia.

Chronic pancreatitis is an irreversible inflammatory process leading to the destruction and fibrosis of the pancreatic parenchyma and formation of pancreatic duct strictures. Endoscopic diagnostics can be considered in patients were non-invasive imaging and functional diagnostics of exocrine or endocrine dysfunction of the pancreas didn't lead to diagnosis. EUS is the best method for diagnosing chronic pancreatitis by assessing changes in the parenchyma of the gland (hyperehogenic areas, lobularity and cysts) and enables good imaging of the pancreatic ductal system (dilation of the main pancreatic duct, irregularities in the duct, hyperechogenic wall and pancreatolites). In the absence of characteristic features, we can reliably exclude chronic pancreatitis. As some morphologic features of acute and chronic pancreatitis are similar, EUS should be performed at least 4 weeks after acute pancreatitis resolution. In the past, ERCP and contrast pancreatography were the gold standard of diagnosis of chronic pancreatitis, with characteristic features of the pancreatic ductal system described by the Cambridge classification. Due to the invasiveness of the procedure and the risk of acute exacerbation after ERCP, it was replaced by non-invasive methods (MRCP and EUS). ERCP maintains the main therapeutic procedure in resolving pancreatic duct strictures (dilatation and stenting), removal of pancreatoliths, and less often in the acquisition of cytological samples (brushing and biopsy). Small pancreatoliths are treated with extracorporeal shock wave lithotripsy (ESWL), which is effective in 90% of patients. In pancreatoliths larger than 5 mm, ESWL is followed by ERCP and endoscopic removal of pancreatoliths. If ESWL is not successful or feasible, intraductal mechanical lithotripsy may be considered. Endoscopic treatment is less effective as surgery, however as it is considerably less invasive, it is recommended as first line treatment (it can resolve symptoms in about a third of patients). The dominant stricture of the main pancreatic duct is treated with ERCP and dilatation of the stricture and insertion of 10Fr plastic stent. If stricture persists, placement of additional stents is advised. Placement of uncovered self-expanding metal stents in pancreatic duct is not indicated; there is currently not enough evidence to recommend the insertion of covered self-expanding metal stents. Patients after failed endoscopic treatment are referred to surgery.

ERCP has an important role in conditions where the **major pancreatic duct is damaged** (traumatic injury, iatrogenic damage during surgery or as a result of acute necrotizing pancreatitis) with pancreatogenic ascites or pseudocysts. By ERCP and placement of plastic pancreatic stent the leakage is resolved and the pancreatic duct can heal.

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PANCREATIC DISEASES

Textbook of Selected Topics in Clinical Gastroenterology

NOVELTIES IN SURGICAL TREATMENT OF PANCREATIC DISEASES

David Badovinac*, Aleš Tomažič**
University Medical Centre Ljubljana, Slovenia, Department of Abdominal Surgery

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ABSTRACT
The incidence of different pancreatic diseases in the recent years has been rising worldwide and development of pancreatic surgery has been trying to cope with this trend. Different approaches and various techniques have been proposed and tested in order to treat the patients and minimise the risk of postoperative complications.
In treatment of acute pancreatitis, the step-up approach has been propagated in the past years. The main goal of this approach is the control of the septic focus and it relies on less invasive treatment modalities and minimally invasive surgery. Percutaneous or endoscopic drainage is usually attempted first. When insufficient, minimally invasive retroperitoneal necrosectomy can be performed.
For chronic pancreatitis, different resection techniques have been developed in order to manage chronic pain. Partial pancreatectomies have long been the standard surgical approach, until the Beger procedure was developed – a duodenum-preserving pancreatic head resection with a Roux-en-Y jejunum loop anastomosis. Later, some modifications were developed, but resection technique should be chosen for each patient individually.
Pancreatic cancer remains the most troublesome disease of the pancreas, as the long-term survival in the past decades has only gradually improved. Surgery remains the standard of care with the main goal being negative resection margins. Borderline resectable disease is defined based on different criteria and these patients are first treated with induction chemotherapy. In approaching the resection of borderline cancer, there are more possible techniques, with the artery-first approach being most propagated.

Key words: *surgical treatment, acute pancreatitis, step-up approach, chronic pancreatitis, resection with drainage, pancreatic cancer, pancreaticoduodenectomy, distal pancreatectomy, borderline resectable disease, artery-first approach*

INTRODUCTION

The diversity of pancreatic diseases is enormous and complications they bring are not to be ignored. Worldwide, the incidence of different conditions in the recent years has been on the upswing and development of pancreatic surgery has been trying to cope with this trend. Different approaches and various techniques have been proposed and tested in order to treat the patients and minimise the risk of postoperative complications, but specificity of pancreatic diseases, especially cancer, is making the progress difficult. Despite numerous studies and innovations, the poor long-term survival of patients with pancreatic cancer remains the most worrisome issue. Nevertheless, there are some reports of slight improvement in the overall 5-year relative survival of patients with pancreatic cancer over the past decades (1–3). Furthermore, supportive and perioperative patient care have improved considerably and morbidity and mortality rates after different surgical procedures have consequently fallen.

* David Badinovac, MD
University Medical Centre Ljubljana, Slovenia, Department of Abdominal Surgery, Zaloska 7, Ljubljana, Slovenia.
** Professor Aleš Tomažič, MD, PhD
University Medical Centre Ljubljana, Slovenia, Department of Abdominal Surgery, Zaloska 7, Ljubljana, Slovenia.

This, however, comes at a high price. Pancreatic surgery is not only time-consuming but also very expensive, thus not only further research but also funding is needed in the field.

In this review we aim to highlight the more recent surgical innovations for the three most common pancreatic pathologies and summarise the conclusion of some studies that have evaluated these methods.

ACUTE PANCREATITIS

The incidence of acute pancreatitis in the Western countries has been increasing in the past years (4, 5). Even though the disease is usually mild and self-limiting, severe cases are still associated with high morbidity and mortality (6). Conventional surgical debridement was long propagated early in the course of acute necrotising pancreatitis and thus far open necrosectomy still remains the gold standard. However, the results of such approach are poor, with high mortality and severe postoperative complications (7–9). Therefore, a different, step-up approach was developed and has been widely gaining popularity in the recent years.

Step-up approach

The main goal of the step-up approach is the control of the septic focus (10). It relies on less invasive treatment modalities and minimally invasive surgery and is thus a current alternative to open necrosectomy. The step-up approach allows optimisation of the patients' critical condition and planning of the surgical procedures, yet it has to be tailored to suit each individual case (11).

Initially, percutaneous drainage is usually attempted for treatment of infected pancreatic necrosis, with one or more percutaneous drains inserted under radiological guidance. Alternatively, endoscopic transgastric drainage of the retroperitoneal space can be performed.

Minimally invasive retroperitoneal necrosectomy is an upgrade of the previous techniques. It combines the advantages of the minimally invasive techniques and open necrosectomy, with simultaneously reducing the overall morbidity rate in comparison to the latter (12). The main goal is not removal of all necrosis in the retroperationeal space, but rather the control of the infection. Nonetheless, it is sometimes difficult to achieve sufficient necrosectomy and establish an adequate drainage. Consequently, it is often necessary to repeat the procedure several times. However, if necessary, different procedures may be performed sequentially without the first procedure compromising the later ones, which is often the case in open necrosectomy (11). There are two main approaches of the minimally invasive retroperitoneal necrosectomy (10).

Video-assisted retroperitoneal debridement

Video-assisted retroperitoneal debridement (VARD) combines laparoscopy and a left small open lumbotomy close to the site of percutaneous drain. It is thus considered a hybrid procedure (13). The percutaneous drain is used as a guide to the retroperitoneal space, which is cleared of pus and necrosis under direct visual control. By progression to the deeper parts, a single laparoscopic port can be administered at the incision site, enabling introduction of a videoscope for further improvement of the visualisation of the cavity, which can then be cleared of necrosis with laparoscopic instruments. Removing all the necrosis is not the aim and only large, loose bulks of necrosis are removed, while necrotic areas adherent to the surrounding tissue is left intact This way the risk of blood loss from the viable tissues is reduced. Extensive lavage of the retroperitoneal cavity is then performed and before fascia closure two large drains are placed in the collection. These two drains are used for further extensive lavage in the following days.

Minimal access retroperitoneal pancreatic necrosectomy

Minimal access retroperitoneal pancreatic necrosectomy (MARPN) is another possible way of performing retroperitoneal necrosectomy. To achieve this, a CT-guided pigtail catheter is first inserted into the necrotic cavity by a radiologist. In general anaesthesia, a surgeon then exchanges the catheter over a guide wire and uses renal dilator to achieve a 30 French tunnel. Using foreceps, the necrotic tissue is then removed and a large irrigating drain is put in place. Continuous irrigation of the necrosis cavity is then performed, along with repeated debridement every 7–10 days in local anaesthesia (14).

Regardless of the methods chosen to treat patients with severe acute pancreatitis, a multidisciplinary ap-

proach is always needed, as is also hospitalisation in a specialty centre. Personal experience and institution preferences still play a key role in dealing with these patients.

CHRONIC PANCREATITIS

The main indication for surgical treatment of chronic pancreatitis is unmanageable chronic pain, which cannot be controlled by other means. For that reason, nearly half of all patients with chronic pancreatitis will require surgery at some point (15, 16). Other indications include gastrointestinal or biliary obstructive complications, recurrent episodes of acute pancreatitis and the risk of a developing malignancy (16, 17). Treatment options include surgical drainage with a pancreaticojejunostomy, different kinds of resections or a combination of the two.

Pancreas resections and resections with drainage

Partial pancreatectomies, whether pancreaticoduodenectomy (PD) or distal pancreatectomy (DP), have long been the standard surgical approach. For potential lesions or enlargement of the pancreatic head, a Whipple procedure or pylorus-preserving pancreaticoduodenectomy (PPPD) were routinely performed. Later, the Beger procedure was developed – a duodenum-preserving pancreatic head resection (DPPHR) with a Roux-en-Y jejunum loop anastomosis to the preserved small portion of pancreatic head tissue, adjacent to the bile duct, and the remaining left pancreatic stump (see Figure 1) (18, 19). Two modifications of the original procedure have also been introduced, the Frey and the Berne technique, both avoiding dissection of the pancreas from the superior mesenteric vein (SMV) and the portal vein (PV).

The Frey procedure combines lateral incision of the pancreatic duct over its full length and hollowing out of the inflamed pancreatic head tissue (see Figure 2). The open pancreatic duct and the cavity in pancreatic head are then both drained into a *Roux-en-Y* jejunal loop (21).

The Berne procedure is somewhat different, as it includes subtotal resection of the pancreatic head, with some tissue left towards the PV and the duodenum (see Figure 3). The whole cavity, along with the pancreatic duct, which is widely opened, is again drained into a *Roux-en-Y* jejunal loop (22).

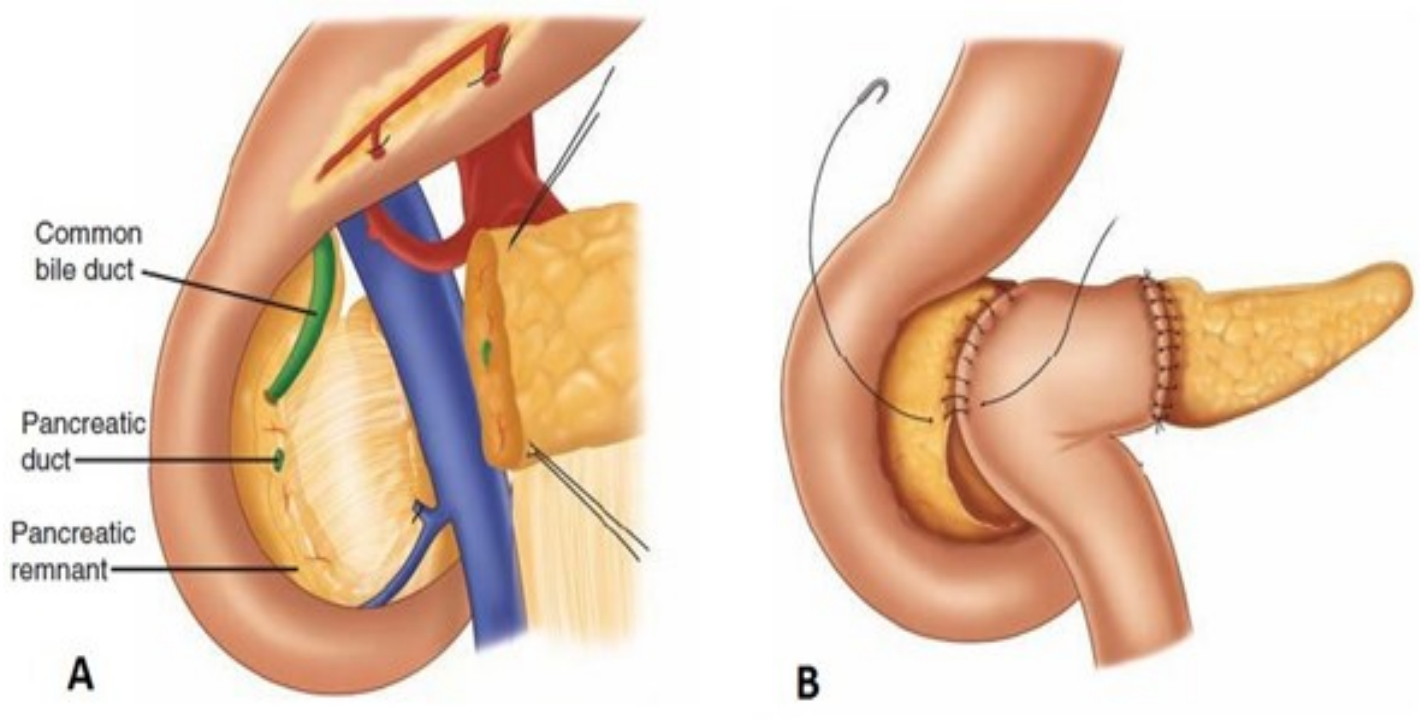

Figure 1: *The Beger procedure; A – transection of the pancreatic neck and subtotal removal of the pancreatic head, with preservation of the duodenum and the common bile duct; B – a Roux-en-Y jejunum loop anastomosis to the remaining portion of the pancreatic head and to the distal pancreas (*20).

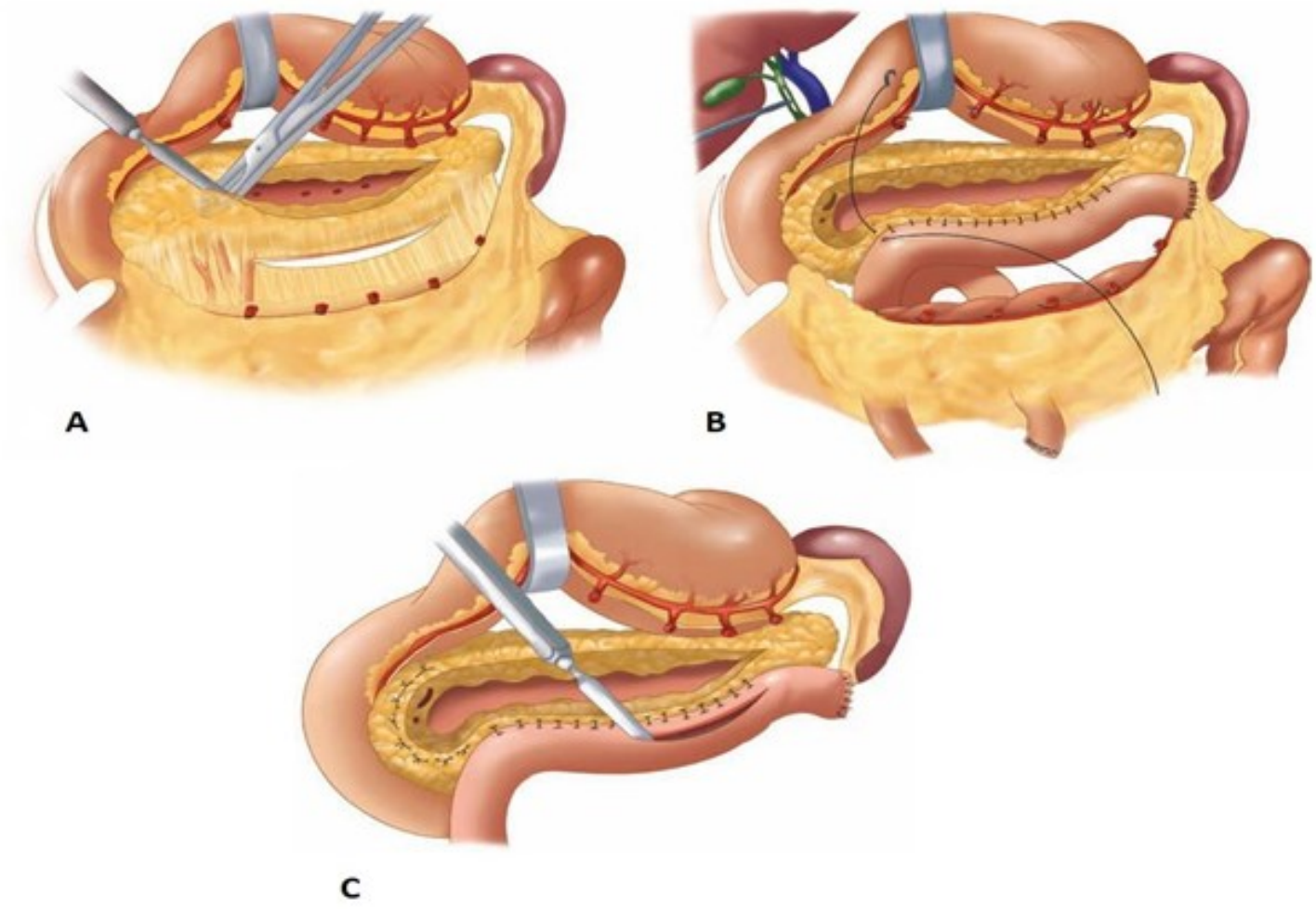

Figure 2: *The Frey procedure; A – local resection of the pancreatic head and lateral incision of the pancreatic duct over its full length; B and C – reconstruction with a side-to-side Roux-en-Y pancreaticojejunostomy* (20).

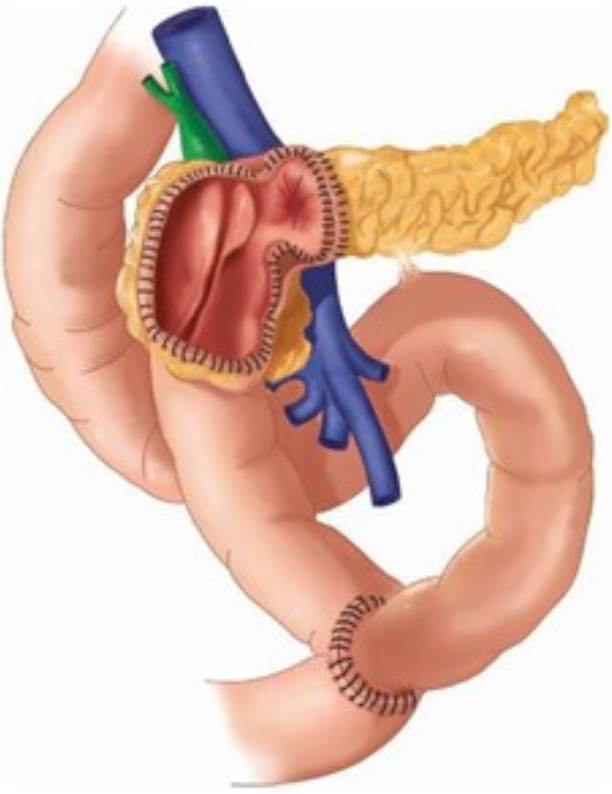

Figure 3: *The Berne procedure; subtotal resection of the pancreatic head with a Roux-en-Y jejunum loop anastomosis to the pancreatic duct and cavity of the resected pancreatic head* (20).

Several studies compared the standard PD with different modifications of DPPHR, and some have suggested superiority of the latter (23). Yet these trials were small and rather inconclusive. However, just recently, a large multicentre randomised controlled trial (ChroPac) performed the same comparison (24). The study suggested that for surgical treatment of chronic head pancreatitis both partial PD and DPPHR are effective and comparable in terms of mortality, morbidity between interventions and quality of life. While operative times in DPPHR were shorter, there were also more readmission in comparison to partial PD, suggesting that partial PD was a more definitive solution. Nonetheless, the resection technique should be chosen for each patient individually and no straightforward recommendations can be made thus far.

Total pancreatectomy with islet auto-transplantation

In patients with genetic pancreatitis, diffuse small duct disease or when lesser surgical treatment was unsuccessful, total pancreatectomy with islet auto-transplantation (TPIAT) may be another option (25). Firstly, to relieve pain, complete pancreas resection is performed. The pancreas is then preserved in a cold balanced electrolyte solution and the vessels are flushed for exsanguination. In controlled laboratory conditions the pancreas is then enzymatically digested and islets are isolated from the excessive tissue. Islet auto-transplantation is then carried out with the aim of reducing the burden of post-surgical diabetes. By infusion into the portal venous system, islets are carried away to settle down in the liver.

TPIAT is reported to improve patients' quality of life and reduce pain symptoms (25–27). Nonetheless, almost 50% of patients require opioids 1 year after surgery, and around 25% 5 years after TPIAT (25, 26). Outcomes of diabetes control are more variable, as 30 –50% of patients soon after TPIAT require no insulin at all, while in some patients transplanted islets fail completely (25, 28).

PANCREATIC CANCER

Surgery in pancreatic cancer remains the standard of care with the main goal being negative resection margins (R0 resection) (29). Resectability of tumours is usually established on the basis of radiological findings, but clinical and biological parametres should also be taken into consideration (30). In order to define tumour resectability, presence of metastatic lesions and evaluation of potential involvement of major blood vessels in the proximity of the lesion must be made on a CT scan. Involvement of the portal vein (PV) and the superior mesenteric vein (SMV), the superior mesenteric artery (SMA), the coeliac axis (CA) and the common hepatic artery (CHA) must be evaluated separately. Only patients amenable to a curative, R0 resection are appropriate candidates for surgical treatment (29).

	Pancreatic head or uncinate process	***Pancreatic body or tail***
Unresectable locally advanced tumours	Tumour contact with the SMA or the CA of >180° Tumour contact with the first jejunal SMA branch Tumour involvement or occlusion of the SMA or the PV, not allowing for safe reconstruction Tumour contact with most proximal draining jejunal branch into SMV	Tumour contact with the SMA or the CA of >180° Tumour contact with the CA and the aorta Tumour involvement or occlusion of the SMA or the PV, not allowing for safe reconstruction

Table 1: *Criteria defining unresectable locally advanced pancreatic cancer* (31).
Legend: SMA – superior mesenteric artery, CA – coeliac axis, SMV – superior mesenteric vein, PV – portal vein.

Resectable tumours

At the time of diagnosis, only 15–20% of tumours are resectable. Presence of any distant metastases, including non-regional lymph nodes metastases, makes pancreatic cancer unresectable. Resectable tumours has no arterial contact, whereas regarding the veins there should be no contact or contact of <180 °C, along with no vein contour irregularities (31). In such cases, an attempt of surgical resection should not be postponed, as resection represents the only possible curative treatment.

Besides 7 negative resection margins (anterior, posterior, medial or SMV groove, along the SMA, bile duct, enteric and pancreatic transaction), adequate lymphadenectomy must be performed. At least 15 lymph nodes must be retrieved from the standard regions (32). Extended lymphadenectomy includes dissection of SMA, CT and hepatic arteries, as well as paraaortic and paracaval lymph nodes (33, 34), yet it is not generally propagated. It does not improve the long-term survival of patients, but it does bring higher risk of postoperative complications, including the occurrence of pancreatic and biliary fistulas (34, 35).

Head and uncinate process

For tumours of the head and uncinate process, PD remains the only option. There are some possible variations of the procedure with the standard Whipple resection (WR) and PPPD being the most common. There is some controversy whether one procedure is superior to the other. While PPPD was thought to lower the incidence of biliary reflux and dumping syndrome (36), the newest evidence suggests there is no difference between WP and PPPD in terms of morbidity, mortality and long-term survival. No significant differences between the two techniques for the occurrence of biliary leakage, postoperative bleeding and pancreatic fistulas was found. Nonetheless, PPPD might have the advantage of reducing operating time, but the benefits for postoperative morbidity remain unclear. (37).

As in DP, minimally invasive approach is gaining its recognition even in cases of PD. There are no randomised controlled trials comparing the open procedure to the laparoscopic one in cases of malignancy. Available studies included both benign and malignant lesions and were all subject to careful patient selection and bias (38, 39). The results demonstrate no difference regarding the post-operative results in terms of hospital stay, mortality, morbidity, re-operation and pancreatic fistula rate. Furthermore, both approaches demonstrated equal results in terms of free resection margin and number of lymph nodes retrieved (40). Although feasible, severely prolonged operative times and technical difficulties of laparoscopic PD raise doubts of the procedure usefulness (39, 41, 42). Despite the rising numbers of laparoscopic pancreas resections, which have tripled in the past 15 years, laparoscopy is used in only 4.3% of PD (43).

Robotic assisted PD is another option of minimally invasive surgical approaches. Despite being very attractive for the reconstruction part of the procedure, along with anastomosis formation, the robotic PD has not been shown to reduce the mortality and the incidence of postoperative complications. Furthermore, operative times are considerably longer and the conversion rate is higher. Taking all of this into account, doubts of further development and training for robotic PD have been raised (44, 45).

Body and tail

Standard treatment procedure for tumours of the pancreas body and tail is distal DP. Resection of the pancreas left to SMA and SMV in needed, as well as splenectomy for assuring adequate lymphadenectomy. More radical approach propagates additional dissection of SMA left to CA (46).

The conventional retrograde DP proceeds in a left-to-right fashion. The spleen and distal pancreas are mobilised first, with pancreas division being performed last. This approach is most commonly used, though it provides late vascular control and limited visualisation of the posterior plane (48, 49).

As an alternative, radical antegrade modular pancreatosplenectomy (RAMPS) has been suggested. Unlike conventional retrograde DP, RAMPS proceeds in a right-to-left fashion. Pancreas is transected early in the course and splenectomy is performed last. This approach provides early control of the splenic vessels and more radical lymphadenectomy. Retroperitoneal dissection plane can be fully visualised, thus R0 resection should be more readily achievable (46, 49, 50).

However, no study has shown improved overall survival with either operative approach (51). Furthermore, there is no difference in the location of tumour recurrence (50).

Regarding minimally invasive surgery, laparoscopic DP is much more widespread than laparoscopic PD. The procedure is already well established for treating benign and premalignant lesions of the pancreatic body or tail and has been gaining recognition in treatment of pancreatic carcinoma as well. The operation is feasible and safe and in some aspects it has been shown to offer even better results than open DP (52). Laparoscopic DP has been shown to reduce blood loss intraoperatively, shorten hospital stay and is comparable or even superior to open DP in terms of lymph node yields and negative resection margin rates (53-55). However, most of the studies reporting this included patients undergoing laparoscopic DP for benign or premalignant lesions and in cases of PDAC, the patients were carefully selected. No randomised controlled studies exist on this matter and therefore, no strong recommendations can be made for laparoscopic treatment of pancreatic body and tail cancer. The duration of surgery is greater and with the exception of the well-known general benefits of a minimally invasive approach, the procedure does not offer improvement in post-operative complications and obvious oncological benefit (56).

Borderline resectable tumours

Defining borderline resectable disease is sometimes difficult and different authors propagate different criteria. Relatively high incidence of occult metastatic lesions complicates the evaluation of resectability even more (57). Internationally most recognised are the criteria launched by the National Comprehensive Cancer Network (NCCN), which are also acknowledged by the European Society for Medical Oncology (ESMO) (see Table 2).

Prior to surgery, treatment of borderline resectable cancer should primarily include induction chemotherapy with gemcitabine or FOLFIRINOX regimen (fluorouracil [5-FU], leucovorin, irinotecan and oxaliplatin). This approach is believed to increase the negative margin and overall resection, as well as survival rate, yet this has not been completely confirmed (58–60) Despite the fact that neoadjuvant treatment downstages borderline resectable pancreatic cancer and makes it amenable for surgery in 40–60% of patients (61, 62), evidence to support such regimen have been sparse (60).

Another issue of borderline resectable disease is resection of the affected blood vessels. As far as the venous involvement, resection of the affected veins has increasingly been performed in order to achieve negative margins (63, 64). It has even been recommended

	Pancreatic head or uncinate process	***Pancreatic body or tail***
Borderline resectable tumour	Tumour contact with the SMA of ≤180° Tumour contact with the CHA, without extension to the CA or the hepatic artery bifurcation, allowing for safe resection/ reconstruction Tumour contact with the SMV or the PV of >180° or contact of ≤180° with contour irregularity or vein thrombosis but with suitable collateral vessels allowing for safe resection/vein reconstruction Tumour contact with the IVC	Tumour contact with the CA of ≤180° Tumour contact with the CA of >180°, without involvement of the aorta and the gastroduodenal artery Tumour contact with the SMV or the PV of >180° or contact of ≤180° with contour irregularity or vein thrombosis but with suitable collateral vessels allowing for safe resection/vein reconstruction Tumour contact with the IVC

Table 2: *Criteria defining borderline resectable pancreatic cancer* (31).
Legend: SMA – superior mesenteric artery, CHA – common hepatic artery, CA – coeliac axis, SMV – superior mesenteric vein, PV – portal vein, IVC – inferior vena cava.

in cases of PV and SMV involvement when safe and R0 resection is feasible. Postoperative morbidity and mortality in case of venous resection and reconstruction are comparable to the standard resection and there is also no difference in long-term survival when R0 resection is achieved (65, 66). On the other hand, arterial resections are generally not encouraged, as they are associated with a higher mortality rate and incidence of postoperative complications (67-69).

Artery-first approach

In approaching the resection of borderline cancer, there are more possible techniques. One of the most widely used is the "artery-first" approach. Allegedly, it reduces intra-operative blood loss and offers a better likelihood of R0 resection (70, 71). Another advantage, especially in borderline cases of pancreatic head tumours with a suspected SMA involvement, is early recognition of actual resectability.

Artery-first approach in DP has, thus far, rarely been advocated (72). On the contrary, for PD there are several variations of the artery-first approach, with the posterior SMA first approach being most common (73). The latter begins by the Kocher manoeuvre and with subsequent retraction of the pancreatic head to the left in order to expose the origin of SMA. Excision of perivascular tissue alongside the SMA and posterior to the head of the pancreas is then performed, followed by dissection of SMA from the uncinated process (70). Posterior SMA first approach may significantly improve lymphatic node yields and improve tumour clearance of the posteromedial area. With a comparable postoperative morbidity and mortality to the standard PD, some have suggested the SMA first approach should also be considered in routine PD (73).

TRIANGLE operation

Recently, another technique has been proposed with the aim of achieving radical resection in cases of borderline resectable PDAC encasing CA or SMA. The so-named TRIANGLE operation includes the artery-first approach, but it also involves extended dissection of CA and SMA. After complete resection and dissection of the adjacent soft tissue is performed, an anatomic triangle is revealed, bordered by the CA, SMA and PV. The technique avoids resection of the encased CA or SMA in cases of locally advanced PDAC, but whether it benefits the long-term survival is yet to be determined (74).

CONCLUSION

The important role of the pancreas in human physiology and the diversity of pancreatic diseases are the driving force of innovations in dealing with them. Degradation of quality of life is what affects patients most. Complications following different pathologies, with morbidity and mortality remaining high, demand constant improvements in diagnostics and therapeutic approaches. However, innovations in the field of surgery are scarce and should be introduced with caution. Most of the trials comparing different approaches offer no clear recommendation and are seldomly conclusive. Nevertheless, the surgeons must strive to evaluate the novelties based on the accessible literature and their own experience and try to implement them in their own practice if they are beneficial for the patients. Measures towards centralisation of pancreatic surgery should be taken and patients should be referred to high-volume centres with experienced surgical teams. The whole field of pancreatology demands new and well-designed clinical trials, thus we should all take as much interest as possible in order to conduct them.

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PANCREATIC DISEASES

Textbook of Selected Topics in Clinical Gastroenterology

SYSTEMIC TREATMENT OF PANCREATIC CANCER

Borut Štabuc*, Gašper Boltežar**
University Medical Centre Ljubljana, Slovenia, Clinical Department of Gastroenterology

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ABSTRACT
The incidence of pancreatic cancer is rising and 357 new patients were recorded in Slovenia in 2009. Surgery remains the only potentially curative treatment and adjuvant therapy brings survival benefit. Treatment of metastatic disease was based on gemcitabine monotherapy for the past 15 years. Recent studies of 5-FU, irinotecan and oxaliplatin regimen (FOLFIRINOX) and gemcitabine combination with nab-paclitaxel show survival benefit and are new first-line treatment options for these patients. Combinations with nal –irinotecan is treatment of choice in second line treatment.

Keywords: *pancreatic cancer, chemotherapy, radiochemotherapy*

INTRODUCTION

Pancreatic cancer is the 10th most common cancer diagnosed and the 4th most common cause of death resulting from cancer. Median survival is approximately three to six months, and only 2% of patients will be alive five years after diagnosis. Incidence rates are virtually identical to mortality rates with a range of 2.1 to 18.5 per 100.000 people. According to the Slovenian Cancer Registry data for 2009, the incidence of pancreatic cancer was 18.5 per 100.000, which means 357 new cases (1).

The only curative treatment of pancreatic cancer is radical surgery, however this type of treatment is possible only with stage I (T1 – T2, N0) and sometimes stage II (T3 N0, T1 – T3, N1) disease. It is well known that age is inappropriate criteria for patient selection and that extended lymphadenectomy brings no survival benefit; among 100 patients with pancreatic cancer, radical resection is possible in 20 patients only. Median survival in this patient group is 15 months and only four patients will be alive at five years. On the other hand, radiation and chemotherapy or best supportive care are the treatment option for 80% of patients with pancreatic cancer. The medium survival in this group of patients is between three and six months and only 2% will be alive at three years.

ADJUVANT CHEMOTHERAPY AND CHEMO-RADIATION THERAPY OF PANCREATIC CANCER

According to the American Gastroenteorology Association medical position statement from 1999, adjuvant therapy with 5-FU based chemo-radiation regimen should be considered after surgical resection(2). This medical position statement was based on one pivotal study, which supports adjuvant chemoradiotherapy in patients with resected pancreatic cancer. This small study that enrolled 43 patients and showed a median survival benefit of 20 months versus 11 months with significant five-year survival difference (18% *versus* 8%) in patients who received bolus 5-FU with radiati-

* Professor Borut Štabuc, MD, PhD
University Medical Centre Ljubljana, Slovenia, Clinical Department of Gastroenterology, Japljeva 2, SI–1000 Ljubljana.
** Gašper Boltežar, MD
University Medical Centre Ljubljana, Slovenia, Clinical Department of Gastroenterology, Japljeva 2, SI–1000 Ljubljana.

on therapy for one year compared to those with who did not (3). Small sample size was the most important weakness of this study.

However, EORTC study in 207 patients with pancreatic and ampullary cancer compared treatment with infusional 5-FU and radiotherapy given in split curses (40 Gy) or observation only and showed only a trend towards benefit of chemoradiation in terms of medium survival (24.5 months *versus* 19 months; p=0.2008) (4). This study was criticized for its radiotherapy component - suboptimal lower dose and split curses.

ESPAC–1 enrolled 541 patients with resected pancreatic cancer comparing, in a complicated trial design, post operative observation, chemoradiation, chemotherapy and chemoradiation followed by chemotherapy. The chemotherapy-only arm showed statistically significant benefit over the observation arm in median survival (20.1 months *versus* 15.5 months; P=0.009), while the chemoradiation therapy arm showed worse median survival (15.9 months *versus* 17.9 months; p=0.05). The main weakness of this study was possible selection bias as patients and clinicians were allowed to select which arm to enter. Additional concern was suboptimal radiotherapy, allowing the final radiotherapy dose to be left to the judgment of the treating radiotherapists (5).

These confusing and inconsistent results of the published randomized trials, which failed to provide clear evidence in support to the use of chemoradiation as adjuvant therapy after pancreatic cancer resection, spawned several new studies. One retrospective study, covering a 30-year period at Mayo clinic, evaluated overall survival of 472 patients after radical (R0) resection of pancreatic cancer. Significantly better survival was observed in patients who received adjuvant chemoradiotherapy (25.2 months) compared to those with no adjuvant treatment (19.2 months, p=0.001). The difference in survival can not be attributed to tumor biology - patients receiving adjuvant therapy had more adverse prognostic factors than those not receiving adjuvant therapy (p=0.001) (6).

Analysis of Prospectively Collected Database at the Johns Hopkins Hospital of 616 patients showed similar effect of adjuvant concurrent FU-based chemoradiotherapy. Results confirmed significant improvement in survival after pancreatic cancer resection. Patients receiving chemoradiotherapy experienced longer median (21.2 *versus* 14.4 months; $P < .001$), 2-year (43.9% *v* 31.9%), and 5-year (20.1% *v* 15.4%) survival in comparison to those who received no adjuvant treatment (7).

In a Randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study, 90 patients were randomly assigned to receive either four cycles of gemcitabine or gemcitabine for two cycles followed by weekly gemcitabine with concurrent radiation (50.4 Gy). Median disease free survival was 12 months in the chemoradiotherapy arm and 11 months in the control arm. Median overall survival was 24 months in both arms. First local recurrence was less frequent in the CRT arm (11% *vs.* 24%) (8).

In the CONKO-001 study, Oettle *et al*. randomized 368 patients with resected pancreatic cancer to gemcitabine chemotherapy for six months, or observation only. This trial showed a statistically significant disease-free survival benefit (13.4 months *versus* 6.9 months; P<0.001) of gemcitabine *versus* observation. Adjuvant treatment with gemcitabine showed a trend toward overall survival benefit (22.1 months *versus* 20.2 months; P=0.06), which was later reported statistically significant (9).

Neoptolemos *et al*. report on ESPAC-3 study in which 1088 patients with an R0/R1 resection for pancreatic ductal adenocarcinoma were randomized within 8 weeks of surgery to receive either bolus 5-FU/leucovorin or gemcitabine for 6 months *versus* observation. The median overall survival of patients treated with gemcitabine did not differ from that of patients treated with 5-FU (23.6 months versus 23.0 months; *p*=0.39) (10). However, safety and dose intensity favored gemcitabine in this study.

Randomized phase III adjuvant chemotherapy study comparing gemcitabine versus S1 in patients with resected pancreatic cancer (JASPAC 01) conducted in Japan enrolled 385 patients. This trial showed significantly higher overall two-year survival of S1 treated patients in comparison to the gemcitabine arm (two-year over all survival 70% (95% confidence interval 63%–76%) versus 53% (46%–60%)).

There was also significant difference in median disease free survival with 23,2 months (95% confidence interval 17,5–32 months) in the S1 arm and 11,2 months (9.7–13.5 months) in the gemcitabine arm (11). Adjuvant chemotherapy with S1 for resected pancreatic cancer patients was shown to be superior to gemcitabine and S1 may be considered new standard treatment after pancreatic cancer resection, especially in Asian population.

Recently published study ESPAC-4 by Neoptolemos *et al.* compared adjuvant chemotherapy with gemcitabine and capecitabine versus gemcitabine alone. This was a phase III multicenter, open-label, randomized study. 730 patients who had undergone a complete macroscopic resection of ductal adenocarcinoma of the pancreas (R0 or R1 resection) were randomly assigned to receive gemcitabine plus capecitabine of gemcitabine alone. The median overall survival for patients in the gemcitabine plus capecitabine group was 28.0 months (95% CI 23.5–31.5) compared with 25.5 months (22.7–27.9) in the gemcitabine group (hazard ratio 0.82 [95% CI 0.68–0.98], p=0.032). They concluded that combination of gemcitabine and capecitabine should be the new standard of care (12).

These trials clearly show the benefit of adjuvant chemotherapy; data regarding radiotherapy is less clear as direct comparisons are rare and it may not be required for majority of patients. Most importantly - it should be noted that we still lack good criteria for selection of patients for surgical treatment. Despite resectability, we still loose 30% of patients with stage 1 and 2 disease after radical surgery in first six months.

NEOADJUVANT TREATMENT OF PANCREATIC CANCER

Neoadjuvant therapy has several potential advantages. Better tumor response is aided by delivery of chemotherapy and /or radiation to an intact and well-vascularized primary tumor, furthermore it provides early treatment of micrometastatic diseases and offers a time interval within which unfavorable tumor biology unmasks and identifies patients in whom surgery would not be of benefit. It can reduce the risk of pancreatic leakage after surgical reconstruction and lower the rate of local recurrences to less than 10%. Despite these advantages, there is no evidence and no clinical trials that would support the administration of chemoterapy and/or chemoradiation in the preoperative period.

The University of Texas MD Anderson Cancer Center evaluated neoadjuvant chemoradiation strategies for resectable pancreatic cancer in a series of nonrandomized phase II trials. The 276 patients enrolled in these trials met identical eligibility criteria, which included objective, computed tomography based determination of resectability and histologic confirmation of PC, and the patients underwent resection with a uniform surgical technique. Median overall survival durations as long as 34 months were observed among the 54–74 % of enrolled patients who completed all therapy, including surgery; in contrast, patients who did not complete treatment had median overall survival times of only 7–11 months (13).

TREATMENT OF LOCALLY ADVANCED PANCREATIC CANCER

The median survival of patients with locally advanced pancreatic cancer is better when compared to metastatic disease. The question of optimal treatment for locally advanced disease remains unresolved. Chemotherapy alone and chemoradiation therapy trials report medium survival of ten months. In the European Union, chemotherapy alone remains standard of care. One recent meta-analysis suggested gemcitabine based chemoradiation therapy may be both, more effective and more toxic than 5-FU based chemoradiation (14).

In a recent prospective clinical trial, presented at ASCO GI 2013, 74 patients with locally advanced pancreatic cancer were randomized after 4 cycles of combination chemotherapy to either gemcitabine or capecitabine radiotherapy arm. The split radiation dose in both arms was 15,4 Gy. Medium overall survival was significantly higher in patients with capecitabine radioterapy arm -15,2 months versus 13,4 months in the Gemcitabine radioterapy arm (p=0. 012). Median progression free survival was also longer in this arm (20 versus 10.4 months). Furthermore, following induction chemotherapy the combination of radiotherapy with capecitabine was significantly less toxic than combination with gemcitabine. The benefit was archived with no compromise in local control and improvement in overall survival.

TREATMENT OF METASTATIC PANCREATIC CANCER

In the last 15 years the gemcitabine in dose 1000 mg per m^2 on weekly schedule has been standard treatment for metastatic pancreatic cancer. In prospective clinical trial conducted by Buris at al in 1997, 126 patients were randomized in two treatment arms with either 5-FU or gemcitabine. The difference in progression free survival and medium overall survival was significant across the two arms (medium overall survival – 5.65 months in gemcitabine versus 4.41 months in 5-FU arm, 1 year survival 18 % in gemcitabine and 2% in 5-FU arm, p=0.002). Furthermore, the survival benefit was accompanied by significant clinical benefit in gemcitabine arm patients (15).

Several trials with combination chemotherapy approaches aimed to improve treatment efficacy in following years. In an attempt to assess the combination of gemcitabine with a fluoropyrimidine, phase III trial was performed, comparing combination chemotherapy with gemcitabine plus capecitabine (GemCap) versus single-agent gemcitabine in 319 patients with advanced or metastatic pancreatic cancer. Patients were randomly assigned to receive either GemCap (oral capecitabine 650 mg/m^2 twice daily on days 1 to 14 plus Gem 1,000 mg/m^2 by 30-minute infusion on days 1 and 8, every 3 weeks) or gemcitabine alone. Median overall survival time was 8.4 and 7.2 months in the GemCap and gemcitabine arms, respectively (p= 0.234). *Post-hoc* analysis in patients with good Karnofsky performance status (score of 90 to 100) showed a significant prolongation of median overall survival in the GemCap arm compared to the gemcitabine monotherapy arm (10.1 v 7.4 months, respectively; p=0.014) (16).

Combination chemotherapy trial with gemcitabine and oxaliplatin in metastatic pancreatic cancer randomized 156 patients into gemcitabine and 157 patients into gemcitabine with oxaliplatin (GemOx) arm. The combination was found to be significantly superior to gemcitabine in terms of response rate (26.8% and 7.1%, respectively; p = 0.044), clinical benefit (42.3% and 8.3%; p = .01), median progression free survival (5.8 and 3.7 months, p = 0.04). One-year survival probability was 27.8% in the gemcitabine arm and 34.7% in the GemOx arm (p =*0*.22). Median overall survival time did not differ significantly and was 7.1 months for gemcitabine monotherapy and 9.0 months for GemOx combination (p=*0*.13; HR 1.20; 95 % CI 0.95 to 1.54) (17).

As showed by another trial with 360 enrolled patients, irinotecan plus gemcitabine combination does not affect overall survival or time to progression when compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer (median overall survival 6.3 months and 6.6 months, respectively) (18).

The first gemcitabine combination regimen, which showed modest improvement in overall survival over gemcitabine monotherapy, was gemcitabine with erlotinib. One-year overall survival of 24% versus 17% was reported for the combination and monotherapy (HR 0.76), respectively. The study also supported the concept of effective EGFR pathway targeting in pancreatic cancer patients (19).

Recently, gemcitabine monotherapy was compared to another promising combination in 342 patients with metastatic pancreatic cancer. They were randomized to either 5-FU, irinotecan, oxaliplatine (FOLFORINOX) combination or gemcitabine monotherapy arm and median overall survival was significantly longer in the FOLFIRINOX arm with 11.1 months as compared with 6.8 months in the gemcitabine arm (p<0.001). Median progression-free survival was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group (p<0.001). Not surprisingly, the FOLFIRINOX regimen was associated with higher rates of grade 3 and 4 toxicities than gemcitabine and 42.5% of patients in the experimental arm received G-CSF and almost 1/4 of the patients had grade 3 or 4 fatigue. 10–15% experienced grade 3 or 4 vomiting, diarrhea, or neuropathy (20).

MPACT recently compared the combination of nab-paclitaxel with gemcitabine, in a international phase III study; 842 patients were randomized and significant survival benefit was reported for the combination in comparison to gemcitabine monotherapy (median overall survival 8.5 versus 6.7 months, respectively). One-year survival was 35% in the experimental and 22% in the control arm, a 5% relative difference. Hematological toxicity and neuropathy levels were acceptable and manageable and the combination of gemcitabine with nab-paclitaxel may be considered a new standard for the

treatment of patients with metastatic pancreatic cancer (21).

Until recently, no chemotherapy was approved for patients with disease progression on first line treatment. Wang-Gillam et al. however, proved that nanoliposomal irinotecan combined with fluorouracil and folinic acid extends survival with manageable safety profile. NAPOLI-1 study was a global, randomized, open-label, phase III trial with 417 patient who were randomly assigned either nanoliposomal irinotecan plus fluorouracil and folinic acid, nanoliposomal irinotecan monotherapy or fluorouracil and folinic acid.

Median overall survival in study group was significantly higher in group receiving nanoliposomal irinotecan with fluorourail and flonic acid (6.1 vs 4.2 months, p=0,012). They concluced that nanoliposomal irinotecan represents a valid treatment option for these patients (22).

CONCLUSION

Pancreatic cancer remains a malignancy with grave prognosis. Adjuvant therapy after radical surgery improves patient survival. In metastatic disease, gemcitabine monotherapy remained the main treatment option in the last 15 years. No clear survival benefit was achieved with gemcitabine combination chemotherapy until modest two-week median survival improvement was shown by addition of EGFR-targeting erlotinib. FOLFIRINOX regimen has proven more effective than gemcitabine, however study population selection and unfavorable toxicity profile prohibit its wide use. Nab-paclitaxel combination with gemcitabine has recently emerged as a new standard treatment for metastatic pancreatic cancer with a more favorable safety profile. Nanoliposomal irinotecan combined with fluorouracil and folinic acid was shown to be effective as a valid second line treatment option.

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PANCREATIC DISEASES

Textbook of Selected Topics in Clinical Gastroenterology

PANCREATIC PAIN MANAGEMENT

Neli Vintar*, Katja Režonja**
University Medical Center Ljubljana, Slovenia, Clinical Department for Anesthesiology and Perioperative Intensive Care

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ABSTRACT
The pain relief of pancreatic cancer, of acute and chronic pancreatitis represents a major challenge for pain specialists, gastroenterologists and surgeons and has a devastating effect on patient's quality of life. The models for the pathogenesis of visceral and neuropathic pain are presented.
The ranges of treatment strategies including pharmacological and non-pharmacological methods are reviewed. The pain of chronic pancreatitis remains refractory to effective treatment in many cases and further study and understanding of the underlying pathophysiology are required.

Keywords *pancreatitis, pancreatic cancer, pain, chronic, acute, visceral, neuropathic*

INTRODUCTION

Pain is the cardinal sign of acute pancreatitis. Gradual or sudden pain is severe and persisting. The management of abdominal pain remained one of the most challenging issues also in patients with chronic pancreatitis. It is described as constant pain in the epigastric area with radiation to the back. Pain is intensified after food or alcochol intake. Painful episodes are therefore often accompanied by fatigue, nausea, vomiting, food avoidance, and weight loss.

Pain can be a major problem for people with pancreatic cancer. These cancers can invade and press on nerves near the pancreas. Severe visceral and intensive neuropathic abdominal pain management is very chellenging for gastroenterologists, surgeons and anestesiologists.

PATHOPHYSIOLOGY OF PANCREATIC PAIN

Neuronal tissues within the pancreas and within adjacent structures are affected by the inflammatory process. Recurrent episodes of pancreatic inflammation will involve adjacent structures such as the biliary system, duodenum, stomach and spleen. Current concepts in the pathogenesis of pain in chronic pancreatitis regard neuronal damage leading to peripheral sensitization and resultant central sensitization as fundamental to the development of persistent, often refractory pain in chronic pancreatitis (1).

In the periphery, multiple local mediators such as prostanoids, bradykinin, serotonin, tachykinins and other unknown compounds sustain and contribute to the peripheral sensitization seen in chronic pancreatitis. Nerve growth factor, important in nociceptive sensitization, has increased pancreatic expression in chronic pancreatitis. Trypsin may have direct effects on sensory neurons via the protease-activated receptor 2 (PAR-2). PAR-2 activation has been shown to result in TRPV1 receptor sensitization through capsaicin-evoked release of calcitonin gene related peptide (CGRP) (1).In addition to changes in the periphery,

* Assistant Professor Neli Vintar, MD, PhD
University Medical Center Ljubljana, Slovenia**,** Clinical Department for Anesthesiology and Perioperative Intensive Care, Zaloška 2, SI–1000 Ljubljana.
** Katja Režonja, MD, PhD
University Medical Center Ljubljana, Slovenia**,** Clinical Department for Anesthesiology and Perioperative Intensive Care, Zaloška 2, SI–1000 Ljubljana.

the central nervous system is altered by prolonged and repeated attacks of pain in chronic pancreatitis.

NEUROIMMUNOLOGY

Fregni and coworkers found out that total pancreatectomy fails to relieve pain in up to 30% of chronic pancreatitis patients (2). They hypothesize that there must be a role for a pancreas-independent mechanism in the unremitting pain seen in chronic pancreatitis. They further hypothesize that, in addition to anatomical and neuronal factors modulating pain, the immune system is involved in a 'salutogenic' mechanism perpetuating cycles of inflammation and ongoing pain – a salutogenic response being modulation of the immune response by centres in the brain. Therefore, one could enhance the function of the immune system to promote healing of the inflamed pancreas. What might occur instead is that abnormal immune processes, linked to brain-mediated mechanisms, sustain the visceral inflammation and prolong the duration of pain. This process is ultimately a maladaptive brain response and they consider that fresh approaches to treating the pain of chronic pancreatitis are necessary. They propose that transcranial magnetic stimulation needs further evaluation as a treatment option in the management of chronic pancreatitis.

VISCERAL PAIN IN PANCREATIC DESEASES

The functional properties of visceral nociceptors are different from those of their somatic counterparts and the microenvironments where visceral nociceptors are located, and especially the motor and secretory functions of organs like the gut, play a key role in the activation and sensitization of visceral sensory receptors. All forms of visceral pain include the development of a hyperalgesic state that originates from the internal organ that has been damaged or inflamed and is referred to a remote and superficial region of the body. In some cases visceral hyperalgesia appears in the absence of an identifiable peripheral cause, perhaps as a consequence of the sensitization and hyperexcitability of visceral afferents evoked by subclinical changes in their microenvironment. Hyperalgesia is the most prominent feature of the visceral pain process and is the expression of hypersensitivity of the pain pathway induced by the sensitization of the peripheral receptors that signal visceral sensory events or of the neurons that transmit and process this sensory information to the CNS. A process of synaptic plasticity, of which several molecular components have already been identified, mediates the central amplification of the visceral afferent signals that leads to the hypersensitivity of central neurons. In addition to the hyperalgesia triggered as a consequence of the injury or inflammation of an internal organ (pancreas), there are also functional pain states, characterized by pain reported from the abdominal or pelvic cavities but in the absence of a demonstrable peripheral cause. Although not much is known about the causes of such states it is thought that hypersensitivity of peripheral sensory receptors or an enhanced responsiveness of central visceral pathways may be responsible for such functional pain states.

ABDOMINAL NEUROPATHIC PAIN

In addition to the constant background pain, patients universally describe an 'extra' pain. It may be described as the 'bad' pain that comes unexpectedly, without warning, 'out of the blue'. If patients are unable to control this pain with their usual analgesic regime, the end result is usually a hospital admission. Areas of hyperalgesia and allodynia can be demonstrated in those patients who have had surgery, but also in those awaiting surgery. Pancreatic pain has some of the features of somatic pain, as well as some of visceral pain, but the neuropathic component of pain is often under-diagnosed and under-treated. The characteristics of the severe, sudden, unexpected pain experienced by patients with pancreatic pain are indistinguishable from those seen in many other neuropathic pain syndromes. Detailed history-taking and specific questions looking for, in particular, neuropathic symptoms are essential in guiding therapy.

NEUROPLASTICITY AND SUPRASPINAL MODULATION

There is a growing body of evidence that neuroplastic changes such as those seen in neuropathic pain and other chronic pain disorders may be of importance. The current findings of cortical reorganization in the insula together with reduced evoked potential latency support the theory that cortical reorganization is a mechanism involved in patients with chronic pancreatitis. This insight may lead to changes in the current concept for treatment of pain originating from the pancreas, and medications affecting central hyperexcitability and neuroplastic changes may be of major value.

Dimcevski and colleagues measured electroencephalography traces in patients with chronic pancreatitis, who received electrical stimulation of the oesophagus, stomach and duodenum via an endoscope (3). They recorded changes in the limbic system and in cortical centres such as the anterior cingulate cortex. They concluded that chronic pancreatitis leads to changes in cortical projections of the nociceptive system. Further understanding of these processes may lead to a more targeted approach in terms of the choice of analgesic therapies.

PAIN MANAGEMENT STRATEGIES

Multimodal and interdisciplinary treatment strategies are used for pancreatic pain relief. Nonpharmacological and medical therapies are combined and tailored to patients needs. Patient's collaboration and collaboration of family members are crucial for successful results.

Lifestyle changes are suggested, it is strongly advised to avoid alcohol consumption even to patients who have other causes for chronic pancreatitis. Patients are encouraged to stop smoking. Low-fat diets, vitamin supplements and antioxidant therapies are all recommended in chronic pancreatitis.

Support groups give the opportunity to patients to share their experience with chronic pancreatitis . Patients often share knowledge as to the best analgesics available or new treatments they have tried. Chronic pancreatitis is a condition with no clear-cut reliable treatment strategies and most patients have tried many different therapies. Because of the impact of ongoing chronic disease, many patients with chronic pancreatitis have complex social and marital/relationship situations. They can often become isolated socially, and peer support groups can be invaluable in helping patients with the difficulties that arise from their symptoms.

Chronic pain is a desease per se. Inspite of different pain treatments, the pain persists. With **psychological approaches** we help the patient to accept treatment strategies , improve pain tolerance and starts a new quality of life.

MEDICAL PAIN MANAGEMENT

Many drugs are given alongside analgesics to combat exocrine and endocrine disorders, nutritional deficiencies and concomitant gastrointestinal symptoms (e.g. nausea, bloating). Non-pharmacological interventions, such as endoscopic sphincterotomy, insertion of pancreatic duct stents and removal of pancreatic stones, also come within the category of medical therapy (1).

The World Health Organization (WHO) analgesic ladder provides a logical and consistent framework for the initiation of analgesic medication in the management of pancreatic pain (4).

The approach in establishing an oral analgesia maintenance regime in the patient with pancreatic pain should emphasize simplicity and safety. *One* drug should be chosen from each drug category, a multimodal approach should be used, adjuncts should be used appropriately and medical therapy should be maximized (e.g. enzyme supplementation, proton pump inhibitors, diabetic control, octreotide, antioxidants).

Nonopioid of choice for visceral pain is metamizol. Maximal daily oral dose is 3000 mg to 4000 mg, given in doses of 1000 mg / 6–8 h.

For **acute pain relief** metamizol is given i.v. 1000 mg to 1500 mg, possibly in 100 ml of saline slowly 10–20 min. If needed, opioids are added, for moderate pain tramadol in maximal daily dose up to 400 mg. For severe pain strong opioids are given i.v., in Slovenia piritramid is traditionally administered for pain relief. It can be titrated in boluses 3-5mg i.v. or administered in continuous i.v. infusion 3–5 mg / hr plus boli on demand.

For **chronic pain** the decision to embark on long-term use of strong opioids should be taken only when other measures have failed or are inadequate (5, 6, 7). The use of immediate-release opioid preparations should be restricted to ‘breakthrough’ pain only and should be kept to a minimum. The use of these preparations leads to peaks and troughs in the plasma concentration of the opioid. If episodes of breakthrough pain are becoming more severe or more frequent, the dose of the long-acting medication should be reviewed first. The

majority of the opioid dose should be administered in a slow- or modified-release formulation.

The use of strong opioids in chronic pancreatitis is controversial and undoubtedly carries risk in a group of patients, many of whom have had a history of alcohol or drug misuse. There is a risk of addiction or opioid-seeking behaviour developing. There is the additional danger of accidental overdose of prescribed medication if it is taken in combination with alcohol or other recreational drugs. Close monitoring of drug dose and avoidance of dose escalation help to minimize this risk.

In the case of strong opioids, it is strongly recommended that there is a single prescriber (usually the general practitioner), that the dispensing of the drug by the pharmacist is monitored to avoid stockpiling and there are strong lines of communication between hospital specialists and general practitioners to maintain consistency of prescriptions. Constipation is an important side-effect in any patient on long-term opioids. It can confuse the clinical picture of pancreatic desease by worsening abdominal pain and bloating. Conversely, many patients, despite opioid use, still experience diarrhoea as a result of the malabsorption commonplace in chronic pancreatitis. All opioid-related side-effects should be monitored regularly and specific questions should be asked at regular outpatient or primary care consultations.

There is a growing body of evidence to suggest that peripheral and central sensitization of the pain are important in magnifying the pancreatic pain and that spinal cord and cortical reorganization occurs. Allodynia and hyperalgesia have been demonstrated. For neuropathic pain management pregabalin and duloxetin or gabapentin and amytriptillin are recommended (8). Not only will this help to alleviate neuropathic symptoms, the use of pregabalin or gabapentin stabilizes opioid usage and delays or prevents dangerous dose escalation and opioid-induced hyperalgesia.
The use of ketamine is also an option in the management of neuropathic pancreatic pain. Hyperalgesia can be modulated by the use of an infusion of S-ketamine. In an outpatinet setting, 25mg - 50 mg ketamin and midazolam 2–3 mg , are diluted in 100 ml saline and administered approximately 3hrs (30 ml/hrs). Patients are continuously monitored (ECG, BP and SaO2).
For persistent severe neuropathic pain, patient can be given i.v. infusion of lidocaine (100–150 mg in 50 ml saline, infused 3 hrs 15 ml/h, during infusion ECG monitoring obligatory!).
For cancer patients' ketamine, midazolam and lidocaine are combined with opioids and other drugs in the analgesic mixture for continuous s.c. infusion via elastomeric pumps.

WAYS OF ANALGESIC DRUGS ADMINISTRATION

First option is always **oral administration**. **Subcutaneous** or **intravenous** administration is chosen in cases of swallowing disorders or bowel disfuntion (diarrhoea, ileus), in patients with cognitive disorders or patients taking many different therapies. Subcutaneous infusion can be safely adminstrated at home. For adequate titration of opioid dosage and optimisation of drug combination (metoclopramide, dexamethason, ketamine, lidocaine) patients are often admitted to hospital for some days.

Epidural or **intrathecal** analgesia are advanced invasive methods of analgesic administration. Epidural or intrathecal catheters are inserted by anaesthesiologist, patients are often hospitalized for titration and optimization of analgesic doses and combinations.

Coeliac plexus block is a regional technique that can be performed directly at the time of pancreatic surgery, transcutaneous approach is using anatomical landmarks, modern approaches are CT-guided and endoscopic ultrasound (EUS)-guided coeliac plexus block. Separate reviews by Kaufman et al in 2010 and Puli et al in 2009 demonstrated that EUS-guided coeliac plexus block can be effective in treating pain in chronic non-malignant and malignant pancreatic pain (9, 10). In Slovenia we have limited experiences with coeliac plexus blocks.

Thoracoscopic splanhnicectomy is an invasive surgical denervation method in palliating the pain of patients with chronic pancreatitis; several ribs are removed during the procedure. Possible and often side effects include postural hypotension, interscostal neuralgia and diarrhoea. It is an effective but not longlasting method, so it is performed only in a few centers (11).

ANTIOXIDANTS FOR PAIN RELIEF IN CHRONIC PANCREATITIS

Due to malabsorbtion and also to insufficient food intake because of pain, patients with chronic pancreatitis often develop antioxidant insuficiency. Current evidence shows that antioxidants (vitamin C, vitamin E, flavonoids) can reduce pain slightly. The clinical relevance of this small reduction is uncertain. Adverse events in one of six patients may prevent the use of antioxidants. Effects of antioxidants on other outcome measures, such as use of analgesics, exacerbation of pancreatitis and quality of life remain uncertain so further studies with more evidence are needed (12).

Endoscopic and open surgery for pancreatic pain relief is discussed elsewhere. Surgery brings specific risks. There may be ongoing post-surgical pain from a large wound and the associated drain sites. Chronic wound pain may occur months or years after surgery. Although many patients with chronic pancreatitis improve after surgery, a significant number do not. Extensive pre-operative counselling, before the decision to undergo surgery is made, is essential to clarify the risks and benefits of surgery (1).

CONCLUSION

Pancreatic desease and the accompaning pain have a devastating effect on patient's quality of life. Pain that some describe as unbearable, relentless and all consuming can dominate every aspect of their life. Non-opioids remain first choice analgesics, but opioids as part analgesic regimen for severe pain relief still have an important role and cause several opioid related side effects and risks. Close monitoring of opioid usage as well as consistent prescribing is fundamental to preserving patient's safety.

Effective treatment of underlying pancreatic desease and pain management can only be achieved by interdisciplinary approach. Collaboration of different experts is crucial.

Inspite of different pain management strategies available, pancreatic pain often remains unsuccessfully treated. Further studies are needed to improve our understanding of the pathophisyology of the underlying desease and concommitant pain, which will help us to treat also the intractable pancreatic pain.

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PANCREATIC DISEASES

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EXOCRINE PANCREATIC INSUFFICIENCY

Rado Janša*
University Medical Centre Ljubljana, Slovenia, Clinical Department of Gastroenterology

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ABSTRACT
Exocrine pancreatic insufficiency (EPI) is a medical condition which is characterized by reduced secretion of pancreatic enzymes in the alimentary tract. In certain disease states of the gastrointestinal tract, especially after surgery, however, the secretion of enzymes may be normal, but they don't come in contact with the nutrients at the right time. All this leads to maldigestion and consequent malabsorption and malnutrition. The secretion of pancreatic enzymes is dependent on hormonal and neural signals; a malfunction of the secretory functions can occur in several different ways. The reasons for EPI can be divided into: pancreatic or primary**,** and non-pancreatic or secondary. EPI is often overlooked, particularly in conditions outside the pancreas, because the symptoms are often non-significant. Only in the most severe forms of EPI is steatorrhea present. EPI is diagnosed based on the clinical picture and pancreatic function tests, which are divided into direct and indirect. The basis of the treatment represents a pancreatic enzyme replacement therapy; however, it is also important to introduce a change in lifestyle and an additional intake of vitamin preparations. Long-term targets for the treatment of EPI are: introduction of a change in the diet, treatment of symptoms and treatment of the underlying disease, whenever possible.

Keywords: *pancreas, exocrine pancreatic insufficiency, diagnosis, symptoms, treatment of EPI*

INTRODUCTION

Adverse food reactions are common complaints with increasing prevalence that affect both children and adults. They occur in affected individuals after ingestion of food, which otherwise does not induce any disturbances in healthy individuals. Adverse food reactions could be induced by different kinds of food and by different pathogenic mechanisms, however their clinical presentations are similar and often nonspecific, making diagnosis challenging. Mechanism of these reaction**s** can have an immunological basis (food allergy, celiac disease) or a non-immunological basis (food intolerance).

Food allergy is an adverse immune response driven by Ig E antibodies towards food proteins, whereas celiac disease is immune-mediated enteropathy triggered by the ingestion of gluten. Beside non-immunological, most common causes are food poisoning, infection of gastrointestinal tract, deficiency of a digestive enzyme etc. A common but perhaps underestimated reason for adverse food reaction is also a failure of pancreatic exocrine tissue.

Exocrine pancreatic insufficiency (EPI) is characterized by a deficiency of exocrine pancreatic enzymes to level that is inadequate to maintain normal digestive process. Maldigestion because of impaired luminal phase of digestion causes malabsorption of nutrient and lead to poor nutrition (1). EPI is etiologically heterogenous condition. The leading cause of EPI is primary pancreatic disease, although many conditions can indirectly impair pancreatic exocrine function (secondary EPI) (1–4). An estimated prevalence of EPI in general population is 8/100.000 for men and 2/10.000 for women (5).

Clinical manifestation of EPI varies depending on the stage of disease. The severe form is associated with malnutrition and fat malabsorption shown as steatorrhea, pale, bulky, and malodorous stools, while milder

* Assistant Professor Rado Janša, MD, PhD
University Medical Centre Ljubljana, Clinical Department of Gastroenterology, Japljeva 2, SI–1000 Ljubljana.

forms of disease (faecal elastase 100-200 mcg/g) cause fewer symptoms and are therefore easily overlooked. They show only few unspecific symptoms such as cramps, bloating, abdominal distension and chronic diarrhoea. Diarrhoea results from the presence of osmotically active, poorly absorbed solutes in the bowel lumen that inhibit normal water and electrolyte absorption (6, 7).

Laboratory studies are important in the diagnosis of EPI and reveal a malabsorption syndrome: deficiency of microelements, fat-soluble vitamins and lipoproteins. To confirm the diagnosis of EPI multitude of tests have been developed**,** which directly or indirectly measure pancreatic exocrine function.

Furthermore, studies revealed that EPI has been associated with high morbidity and mortality secondary to malnutrition-related complications and high risk of cardiovascular events. Timely and accurate diagnosing of EPI is hence crucial, because delays in treatment may prolong malnutrition related complications and have important impact on patient's quality of life. Treatment of EPI consists of lifestyle modifications, substitution of deficiencies and compensation for endogenous deficiency with pancreatic enzyme replacement therapy.

PHYSIOLOGY OF EXOCRINE PANCREAS

Pancreas daily secrets about 15.000 ml of colourless, isotonic and alkaline juice with high concentration of pancreatic enzymes, especially lipase. The secretion is under tight neuro-humoral regulation. Secretin and cholecystokinin are the main hormones which regulate pancreas secretion in a negative feedback manner.

Secretin is released from duodenal mucosa as a response to acid gastric juice coming to duodenum from the stomach. Secretin then stimulates the pancreatic interlobular ductal cells to secrete more water and bicarbonate**,** making the pancreatic juice more alkaline and therefore reducing acid level in duodenum.

Another important hormone in regulation of exocrine pancreas is cholecystokinin (CCK). CCK is released from enterocyte's endocrine cell under the presence of fat and proteins in himus. In addition, CCK is also secreted from vagal afferent nerves. CCK directly stimulates release of pancreatic enzyme acting on CCK receptors on acinar cell (see Figure 1).

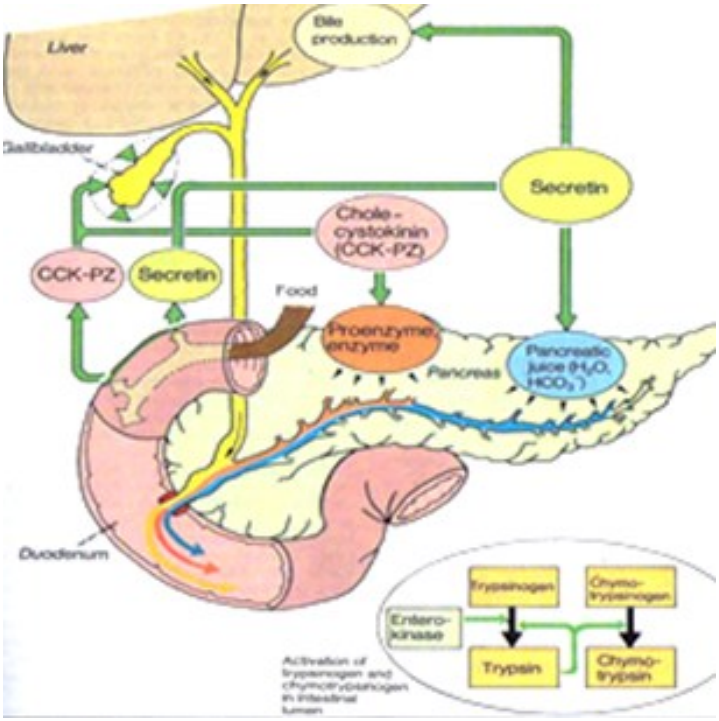

Figure 1: *Physiology of exocrine pancreas.*

ETIOLOGY OF EXOCRINE PANCREATIC INSUFFICIENCY

Exocrine pancreatic insufficiency can be classified as *primary or secondary*. Primary EPI is due to a lack of exocrine pancreatic tissue or disturbances in the innervation. In *secondary* EPI there is impaired exocrine pancreatic function and insufficient enzyme activity (8, 9).

Etiologies of primary EPI:

a. Acute and chronic pancreatitis – most common causes of diverse etiologie;

b. Cystic fibrosis – mutation of the gene that encodes for a chloride channel leads to protein precipitation within the ductal lumen and loss of normal acinar cell function;

c. Diabetes mellitus type 1 and type 2;

d. Obstruction of pancreatic duct (e.g. ampullary or pancreatic cancer);

e. Shwachman-Diamond syndrome (SDS) – rare autosomal recessive disorder characterized by exocrine pancreatic insufficiency, bone marrow dysfunction, leukemia predisposition, and skeletal abnormalities. (10).

Etiologies of secondary EPI:

a. Celiac disease – EIP occurs in about one third of celiac disease patients. We should be aware of EPI when celiac disease resistant to gluten-free diet;

b. Crohn's disease;

c. Zollinger-Ellison syndrome – hypergastrinemia and consequent hyperacidity inactivates pancreatic enzymes;

d. Pancreatic and gastrointestinal surgery – any *surgical procedure* in upper gastrointestinal tract is associated with disturbance of neuro-humoral balance, reduced pancreatic stimulation or loss of pancreatic parenchyma that leads to EPI (5, 11–13).

CLINICAL PICTURE

The hallmark of severe EPI, when more than 90% of acinar cell are destroyed, are steatorrhea and unintentional weight loss (6, 7). However, clinical manifestations of EPI can vary widely, depending on the stage of disease. Clinical features directly reflect the impaired absorption of maldigested nutrients. Patients often complain about nonspecific gastrointestinal symptoms such as watery diarrhoea, flatulence, abdominal discomfort and cramps. Peripheral oedema or even ascites indicates severe protein malabsorption.

A complete laboratory evaluation is crucial in the assessment of a patient with suspected EPI. It determines the extent of malabsorption and assesses manifestations such as hypoalbuminemia, coagulation disorder, osteopenia and anaemia.

Steatorrhea is the result of fat malabsorption and is characterized by pale, bulky, and malodorous stools. These stools often float on top of the toilet water with oily droplets and are difficult to flush.

Another common, yet nonspecific symptom is unintentional weight loss. However, differential diagnosis of weight loss is broad and could be associated with EPI comorbidities or other enteropathy like celiac disease or inflammatory bowel disease.

Flatulence, bloating and abdominal colic occurs when indigested food enters colon and is then fermented by colonic bacteria. Bacterial fermentation of unabsorbed food substances releases gaseous products (hydrogen and methane), which distend intestine, causing flatulence and cramps.

Peripheral oedema may result from hypoalbuminemia caused by protein malabsorption. With severe protein depletion, ascites may develop.

Anaemia resulting from malabsorption can be either microcytic (related to iron deficiency) or macrocytic (related to vitamin B-12 deficiency). Anaemia may also be associated with the underlying disease causing EPI. For instance, iron deficiency anaemia is often a manifestation of celiac disease. Ileal involvement in Crohn disease or ileal resection can cause megaloblastic anaemia due to vitamin B-12 deficiency.

Vitamin K is **a** fat-soluble vitamin which is absorbed with fats and is an essential cofactor in synthesis of coagulation factors. Vitamin K deficiency predisposes patients to haemorrhagic diathesis, which is clinically visible as ecchymosis, though melena and haematuria may occur on occasion. Metabolic bone disease caused by vitamin D deficiency, a core vitamin in calcium regulation, can result in osteopenia or osteoporosis. Rarely, osteomalacia with bone pain and pathologic fracture occur. Persistent low calcium levels lead to compensatory secondary hyperparathyroidism

Other manifestations of fat-soluble vitamin deficiencies are rarely seen today. However, generalized motor weakness is seen with hypovitaminosis D, peripheral neuropathy reflects thiamine deficiency, B12 deficiency causes loss of the sense of vibration and position, hypovitaminosis A provokes night blindness and biotin deficiency is a reason for seizures.

DIAGNOSIS OF EPI

Assessing patient with suspected EPI begins with a comprehensive overview of symptoms, obtaining relevant patient history and a clinical examination. Following that, various tests for EPI are used. These are classified as direct versus indirect measures of exocrine pancreatic function. Many of tests used have poor sensitivity or specificity, especially in investigation of milder forms (see Tabel 1). In everyday clinical practice, the most widely used test is the determination of faecal elastase level. However, secretin MRCP, an indirect test, has been showing promising results and is more extensively used (14). Another non-invasive 13C mixed triglyceride breath test is of limited value, because it is available just at selected few centres, specifically for studying purpose (see Tabel 2).

Secretion of pancreatic enzymes and bicarbonate (Secretin-CCK test)	Fecal Elastase
Mild > 75%	100–200 mcg/g
Moderate 30–75%	50–100 mcg/g
Severe < 30%	<50 mcg/g

Tabel 1: *Classification of EPI based on secretin CKK test and fecal elastase* (1, 5).

	TEST	SENSITIVITY	SPECIFITY
DIRECT STIMULATION	Secretin-CCK test	89–97 %	>90 %
	Lundh's test	88–92 %	>90 %
	Endoscopic secretin test	70–80 %	Not available
	Secretin MRCP	80–85 %	90%
INDIRECT TESTS	Pancreolauryl test	39–100 %	55-100 %
FECAL TEST	**Fecal elastase-1**	37–100 %	93 %
	Chymotrypsin	25–96 %	84 %
BREATH TEST	13C-MTG breath test	70–81 %	Not available

Tabel 2: *Diagnostic specifity and sensitivity of tests for exocrine pancreatic function* (1, 14).

Tests for exocrine function of pancreas:

Direct tests

1. Lundh's test;
2. Stimulation with exogenous hormones;
3. Secretin test;
4. Cholecystokinin (CCK) test;
5. Secretin-CCK test.

Indirect tests

1.Serum trypsinogen

2.Fecal fat test

3.**Fecal chymotrypsin and elastase determination**

4.Pancreo- lauryl test

5.13C mixed triglyceride (13C-MTG) breath test

6.Secretin MRCP

TREATMENT

Treatment of EPI is multimodal and consists of dietary and lifestyle modifications (well-balanced, low fat diet, cessation of alcohol consumption and smoking); substitution of deficient microelements and fat-soluble vitamins; however, the **backbone of treatment is the pancreatic enzyme replacement therapy (PERT)**.

PERT are orally available pancreatic enzymes extracted from porcine pancreas, which could be diagnostic as well as therapeutic. Empiric trail in patient**s** with suspected EPI is in some case indicated without formal testing, because clear response to therapy confirm**s** the diagnosis. Therapeutic goal of PERT therapy is amelioration of symptoms, elimination of malabsorption and prevention of malnutrition - related morbidity and mortality.

The overall daily dose of PERT should be divided between meals (for example 3 meals and 2 snacks, at which the dose for a snack is a half of that for a meal). Appropriate initial dose starts at 40.000–80.000 units of lipase per meal, and 10.000–20.000 units per snack. According to EPI severity and persistence of symptoms, the dose is up-titrated to the maximum daily dose of 10000 units of lipase/per mass/day (15). In patients with EPI and an incomplete response to PERT, an addition of proton pump inhibitor (PPI) can lead to enhanced PERT efficiency and an improvement of response to treatment (1).

PERT is considered to have an overall safety and tolerability profile with only few side effects. Among

them, the most common is constipation, which is often self-limiting (1).

CONCLUSION

Early diagnosis of EIP is of great importance as delay prolongs malnutrition related complications, increase morbidity and mortality and lowers quality of life. Diagnosis of EPI remains a challenge in mild-to-moderate forms of the condition, due to the lack of a reliable test available. Mild-to- moderate forms are therefore often diagnosed late. Another reason for missed diagnosis seems to be secondary EPI, due to many non-pancreatic conditions that indirectly affect exocrine pancreases like diabetes, cystic fibrosis pancreatic cancer etc. In these conditions EPI should be considered as possible cause of gastrointestinal symptoms. When diagnosis of EPI is made, it is necessary to initiate PERT. Treatment with PERT leads to improved nutrition, resolving malabsorption and increased quality of life and last, but not the least, it has significant influence on individual's immunity.

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PANCREATIC DISEASES

Textbook of Selected Topics in Clinical Gastroenterology

NUTRITION IN ACUTE AND CHRONIC PANCREATITIS

Sanela Banović*
University Medical Centre Ljubljana, Slovenia, Clinical Department of Gastroenterology

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ABSTRACT
Nutritional support is different in acute and chronic pancreatitis. Enteral nutrition is unnecessary if the patient can consume normal food after 5-7 days. On the other side, EN should be established in patients with severe (necrotizing) pancreatitis.
In chronic pancreatitis, about 80% of patients can be managed by analgesics, dietary recommendations and pancreatic enzyme supplements. 10–15% need oral nutritional supplements, 5% need enteral tube feeding and almost 1% require parenteral nutrition.

Keywords: *nutrition, acute and chronic pancreatitis, guidelines*

ACUTE PANCREATITIS

The two major forms of inflammatory pancreatic diseases – acute and chronic pancreatitis – are different entities which require different nutritional approaches. It is generally accepted that nutritional management depends on the underlying pancreatic disease. Approximately 75% of the patients with acute pancreatitis have a mild disease with a mortality rate well below 1% (31) as classified by the Atlanta criteria (32).

The majority of these patients can be managed with standard supportive measures that do not need special nutritional treatment; most will resume a normal diet within 3–7 days. The mortality for mild-to-moderate pancreatitis is low, but increases to 19-30% for severe pancreatitis. Mortality approaches 50% if necrosis of the pancreatic gland is more than 50% and can increase up to 80% if sepsis occurs. Approximately half of the deaths in acute pancreatitis occur within the first two weeks of illness and are mainly attributed to organ failure. The remaining 50% of deaths occur weeks-to-months after this period and are related to organ failure associated with infective necrosis.

Nutrition support - indication

1. Mild pancreatitis:

a) step I (2–5 days) – fasting: treat the cause of pancreatitis, i.v. replacement of fluid and electrolytes and analgesics;

b) step II (3–7 days) – refeeding: diet rich in carbohydrates, moderate in protein and fat;

c) step III –no pain and normal enzymes: normal diet.

2**. Severe necrotizing pancreatitis** – enteral nutrition is indicated first if possible. Enteral feeding has been shown to reduce catabolism and the loss of lean body mass, modulate the acute phase response, preserve visceral protein metabolism and have the potential to downregulate the splanchnic cytokine response. If complete enteral nutrition is not possible, nutritional support should be combined with parenteral nutrition.

STEPS:

1. Start with aggressive fluid resuscitation;
2. Try to start with continuous enteral jejunal feeding over 24h with a polymeric–, elemental-or immune -enhancing diet;

* Sanela Banović, MD,
University Medical Centre Ljubljana, Slovenia, Clinical Department of Gastroenterology, Japljeva 2, SI–1000 Ljubljana.

3. If side effects occur or the caloric goal cannot be achieved, TPN should be combined with enteral nutrition;

4. If enteral nutrition is not possible (e.g. prolonged paralytic ileus), TPN should be given with a small amount of an elemental diet infused continuously into the jejunum according to tolerance (less 10-30 ml/h)

5. The use of intravenous lipids as part of parenteral nutrition is safe when hypertriglyceridemia (412 mmol/l) is avoided.

Enteral nutrition: The use of early enteral feeding in patients with severe disease decreases, however, the incidence of nosocomial infection, reduces the duration of SIRS and decreases the overall disease severity. Decisions involved in nutritional management are therefore driven by the disease severity. Greater severity of the disease dictates the need for nutritional support and predicts those patients with acute pancreatitis which most likely will benefit from nutritional therapy. Several factors remain to be clarified: optimal timing of nutritional therapy, route of administration (jejunum or duodenum? stomach?) or parenteral and nutrient formulations remain uncertain at present due to the lack of controlled clinical trials in order to define optimal nutritional therapy. It is clear, however, that enteral feeding is safe; jejunal tubes are well tolerated without an exacerbation of pancreatitis-related symptoms. When the caloric goal with enteral nutrition is not possible, parenteral nutrition should be used.

Parenteral nutrition: Total parenteral nutrition has been the standard treatment for providing nutrients to patients with severe acute pancreatitis. The concept behind this strategy was two-fold: firstly, to avoid stimulation of exocrine pancreatic secretory responses ('to put the pancreas at rest') and secondly, to improve the nutritional status of the patient. The evidence in favor of intravenous feeding is, however, not supported by clinical trials. Two clinical prospective studies have been performed on the use of parenteral nutrition in acute pancreatitis. The study of McClave et al. compared nasojejunal feeding with total parenteral nutrition showing no difference on the outcome but the costs for enteral nutrition was four times lower. In the study of Sax et al., intravenous feeding was compared with no nutritional support. The results demonstrated that intravenous nutrition did not affect the outcome of patients with mild-to-moderate pancreatitis as defined by complication rate, days of oral food intake, or by the total hospital stay. However, an increase in catheter-related infections was observed in the patients receiving total parenteral nutrition. These data indicate that total parenteral nutrition is associated with certain disadvantages. Besides the increased risk of catheter-related sepsis, severe hyperglycemia and other metabolic disturbances have been reported. It is clear, therefore, that overfeeding is a major risk factor for complications in patients receiving parenteral nutrition. In recent years, more concern has been expressed about the possibility of parenteral nutrition adversely affecting gut barrier function. Whilst there is more evidence to support this hypothesis in animals there is tenuous little evidence in clinical practice

Nutrient requirements (mild AP): K energy B25–35 kcal/kg BW/day; K protein 1.2–1.5 g/kg BW/day; carbohydrates 3–6 g/kg BW/day corresponding to blood glucose concentration (aim: o10 mmol/l); K lipids up to 2 g/kg BW/day corresponding to blood triglyceride concentration (aim: o12 mmol/l):

If the course of the disease is complicated by an MOF syndrome, then the calorie and protein requirements have to be adapted. Lower protein loads B1.2 g/kg/day should be given to patients with renal or hepatic failure. Monitoring urinary urea excretion may help to meet actual nitrogen requirements.

Nutrient requirements (necrotising AP): energy 15-20 kcal/kg BW/day- in early phase of catabolism, protein 1,2-1,5 g/kg BW/day – in case of acute liver failure 1 g/kg TT/per day, carbohydrates 36 g/kg ideal BMI (need to control blood glucose), lipids to 2 g/kg ideal BMI (blood triglyceride concentration).

CHRONIC PANCREATITIS

Chronic pancreatitis (CP) is an inflammatory disorder that causes irreversible anatomical changes and damage, including infiltration of inflammatory cells, fibrosis and calcification of the pancreas with destruction of the glandular structure and thereby affects normal digestion and absorption of nutrients.

Maldigestion is often a late complication of CP and depends on the severity of the underlying disease. The medium latency between onset of first symptoms and

signs of maldigestion is about 8–9 years in alcoholic CP and more than 15 years in idiopathic non-alcoholic pancreatitis. Nutrient deficiencies are common in CP, driven by many risk factors including malabsorption, diabetes and, in alcoholic CP, alcoholism. However, deficiencies are frequently overlooked, leading to malnutrition.

During the course of chronic pancreatitis, enzyme secretion is decreased, resulting in maldigestion with steatorrhoea and azotorrhoea. Deficiencies of fat-soluble vitamins are the consequence of steatorrhoea.

About 80% of patients can be managed by analgesics, dietary recommendations and pancreatic enzyme supplements, 10–15% need oral nutrition supplements, 5% need enteral tube feeding and less of 1% need parenteral nutrition.

Nutrient requirements – active patients: 30-35 kcal/kg TT/per day. Patients in hospital: 20-25 kal/kg TT/per day. Protein: 1-1,5 g/kg TT/per day. Lipids must also be given to reach the necessay caloric goal. Up to 30-40% of the calories given as fat are well tolerated, especially if they are rich in vegetable fats.

Fat-soluble vitamins (A, D, E, K), vitamin B12 and other micronutrients should be supplemented if serum levels indicate deficiencies. Low fibre diet is recommended because fibre may absorb enzymes and delay the absorption of nutrients.

Weight control, symptomatic relief of steatorrhoea or a decrease in 72-h fecal fat excretion are practical endpoints for therapy. If the response to enzyme treatment is not satisfactory, addition of an acid inhibitor can be tried. Decreasing the duodenal acid load can prevent the inactivation of lipase in the small bowel.

In general, enteral nutrition is indicated if patients have insufficient intake of calories. The cause of inadequate consumption of calories can be anatomical (pyloroduodenal stenosis), ongoing inflammation, acute complications or fasting due to repeated surgical interventions. It has been shown that continuous overnight delivery of nutrients is suitable.

Enteral nutrition support before pancreatic surgery can be very useful. Data from patients undergoing abdominal surgery have provided evidence that preoperative enteral or oral nutrition support with an immune-enhancing diet improves outcome by reducing the prevalence of postoperative infective complications and duration of hospital stay.

Parenteral nutrition is very seldom used in patients with chronic pancreatitis. PN must be instituted if: gastric emptying is blocked, the patient needs gastric decompression, a tube cannot be introduced into the jejunum or complicated fistula s present.

CONCLUSION

Nutrition support is very important in acute and chronic pancreatitis. Nutritional deficiencies can occur in AP and CP. We have oral, enteral and parenteral way of feeding. It is very important to know the metabolism in normal and pathological conditions.

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PANCREATIC DISEASES

Textbook of Selected Topics in Clinical Gastroenterology

PSYCHIATRIC TREATMENT AND SUPPORT FOR CHRONICALLY ILL PATIENTS

Zvezdana Snoj*
Clinic of Integrative Psychiatry and Psycho-oncology EIRINI, Ljubljana, Slovenia

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ABSTRACT
Cancer is a grave chronic disease that affects the patient and their family both physically and psychologically. Despite bio-medical advances, cancer remains a disease that is frequently associated with pain, suffering and death. Clearly, cancer is not just a one-time event that leads to certain death, but is a long-term chronic disease. A number of studies have shown that psychiatric disorders are more common amongst cancer patients. The most common psychiatric disorders include depression and anxiety. In pancreatic cancer of particular interest are symptoms of depression. There has been a long held belief among clinicians that pancreatic cancer patients at times have a history of unexplained depression and distress that preceded the appearance of physical symptoms. There are marked differences in the occurrence of severe depression in both acute and chronic illnesses, which reflect the meaning to the individual patient in terms of threat, disability, pain and other symptoms. It is not uncommon for depressive symptoms to be accompanied by other comorbid psychiatric symptoms and disorder whose occurrence and pattern again relates to the type of illness. Symptoms of depression not only lead to a deterioration in a cancer patients' quality of life, but also represent an independent factor that affects their survival. Depressed cancer patients also suffer a higher rate of recurrence and more pain than patients that do not suffer from depression. It is therefore important that depression is diagnosed in a timely manner and properly treated. Although depression and anxiety disorders are the psychiatric symptoms most common to all cancer and chronically ill patients, they remain largely undetected or are overlooked. These symptoms warrant evaluation and the use of pharmacologic, psychological and social interventions to relieve suffering. Suffering should not be regarded as an "unavoidable" consequence of cancer. Recognition of the treatment of depression in relation to acute and chronic physical illness remains a major challenge for medicine and for those psychiatrists who work with medical patients. The trend followed in recent years clearly stresses the importance for integrating psychosocial aspects into routine medical care. The need for a multidisciplinary approach is highlighted by the fact that physical and emotional component of psychological burden are inextricably mingled in these patients. Without multidisciplinary efforts it is not possible to implement goals of psycho-oncology, palliative care, and "quality of life" into routine care.

Keywords: *depression, anxiety, psychiatric disorders, chronically ill patients, cancer patients, psycho-oncology, treatment, multidisciplinary approach*

* Zvezdana Snoj, MD, PhD
Clinic of Integrative Psychiatry and Psycho-oncology EIRINI, Ljubljana, Slovenia.

PANCREATIC DISEASES

Textbook of Selected Topics in Clinical Gastroenterology

The textbook entitled “Pancreatic Diseases. A Textbook of Selected Topics in Clinical Gastroenterology” comprises of an editorial and 12 chapters, in which the authors discus modern diagnostics as wheel as the management and treatment of patients with pancreatic diseases. The contributions describe the most common and rare clinical conditions that arise because of a malfunction of the pancreas. The textbook describes the etiology of pancreatic diseases, their clinical course, and lists algorithms in modern diagnostic treatments. Special attention is devoted to the treatment of pancreatic diseases; including modern methods of surgical treatment of the most complex pancreatic diseases and the role of systemic treatment of pancreatic cancer. The reader gets comprehensive information on novelties in the diagnostic and therapeutic treatments of patients from different perspectives of medical professions. The textbook also addresses the quality of life of patients with pancreatic diseases from a medical and social point of view. Highlighted is the psychological importance of treating patients with chronic diseases and the role of relatives in maintaining the quality of life of these patients.

The textbook is an important and high quality contribution to the domestic and international multidisciplinary professional public, which focuses on a particularly demanding field of gastroenterology.

Vladka SALAPURA

The textbook “Pancreatic diseases. Textbook of selected topics in Clinical Gastroenterology” presents a thorough illustrated review on the subject. The book consists of an editorial and 12 chapters. Its contents include description of various pathologies, underlying mechanisms, diagnostic procedures and treatments of the diseases and their symptoms. Also, each chapter presents a survey of relevant basic and recent literature on the corresponding subject. The descriptions in the textbook are clear and written in good English language. The textbook collects various aspects on pancreatic diseases valuable for specialists, general medical audience and students.

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