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Clinical Guidelines of the Russian Society of Surgeons, the Russian Gastroenterological Association, the Association of Surgeons-Hepatologists and the Endoscopic Society "REndO" on Diagnostics and Treatment of Chronic Pancreatitis

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Aim: to present modern methods of diagnosis and treatment of chronic pancreatitis for gastroenterologists, general practitioners and physicians.

Chronic pancreatitis (CP) is a long-term inflammatory disease of the pancreas, manifested by irreversible morphological changes in the parenchyma and pancreatic ducts, which cause pain and/or persistent impairment of function. Current concept on the etiology of CP is reflected by the TIGAR-O classification. The criteria for establishing the diagnosis of CP include typical attacks of abdominal pain and/or clinical and laboratory signs of exocrine, endocrine insufficiency with the mandatory detection of characteristic morphological changes (calcifications in the parenchyma and pancreatic ductal stones, dilatation of the main pancreatic duct and its branches). CT, MRCP, and pancreatobiliary endosonography are recommended as the methods of choice to verify the diagnosis of CP. Conservative treatment of patients with CP is provided for symptom relief and prevention of complications. Individual cases with

severe non-interactable abdominal pain, as well as a complicated course of the disease (development of ductal hypertension due to main pancreatic duct stones or strictures, obstructive jaundice caused by compression of the common bile duct, symptomatic postnecrotic cysts, portal hypertension due to compression of the portal vein or thrombosis of the splenic vein, persistent duodenal obstruction, pseudoaneurysm of the celiac trunk basin and the superior mesenteric artery) serve as an indication for endoscopic or surgical treatment. The Guidelines set out modern approaches to the diagnosis, conservative, endoscopic and surgical treatment of CP, and the prevention of its complications.

Conclusion. The implementation of clinical guidelines can contribute to the timely diagnosis and improve the quality of medical care for patients with chronic pancreatitis.

Keywords: pancreas, chronic pancreatitis, diabetes mellitus, pancreatic pseudocyst, pancreatic hypertension, endoscopic stenting of the main pancreatic duct, lateral pancreatojejunostomy

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Клинические рекомендации Российского общества хирургов, Российской гастроэнтерологической ассоциации, Ассоциации хирургов-гепатологов и Эндоскопического общества «РЭндО» по диагностике и лечению хронического панкреатита

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Цель: представить современные методы диагностики и лечения хронического панкреатита для врачей-гастроэнтерологов, врачей общей практики и врачей-терапевтов.

Основное содержание. Хронический панкреатит (ХП) — длительное воспалительное заболевание поджелудочной железы, проявляющееся необратимыми морфологическими изменениями паренхимы и протоков органа, которые вызывают боль и/или стойкое снижение функции. Современные представления об этиологии ХП отражает классификация TIGAR-O. К критериям установления диагноза ХП относят характерные жалобы на приступы абдоминальной боли и/или клинические и лабораторные признаки экзокринной, эндокринной недостаточности при обязательном выявлении достоверных морфологических изменений (кальцификатов в паренхиме и камней в протоках поджелудочной железы, расширения главного панкреатического протока и его ветвей). КТ, МРХПГ и эндосонография панкреатобилиарной зоны рекомендуются как методы выбора для верификации диагноза ХП. Консервативное лечение пациентов с ХП направлено на купирование симптомов и предотвращение развития осложнений. Отдельные случаи с некупируемой болью в животе, а также осложненное течение заболевания (развитие протоковой гипертензии за счет вирсунголитиаза или стриктур протока ПЖ, механической желтухи, обусловленной компрессией холедоха, симптоматических постнекротических кист, портальной гипертензии за счет сдавления конфлюенса воротной вены или тромбоза селезеночной вены, стойкого нарушения пассажа пищи по двенадцатиперстной кишке, ложной аневризмы бассейна чревного ствола и верхней брыжеечной артерии) служат показанием к эндоскопическому или хирургическому лечению. В Рекомендациях представлены современные подходы к диагностике, консервативному, эндоскопическому и хирургическому лечению ХП, профилактике его осложнений.

Заключение. Выполнение клинических рекомендаций может способствовать своевременному установлению диагноза и улучшению качества оказания медицинской помощи пациентам с хроническим панкреатитом.

Ключевые слова: поджелудочная железа, хронический панкреатит, сахарный диабет, псевдокиста поджелудочной железы, панкреатическая гипертензия, эндоскопическое стентирование главного панкреатического протока, продольная панкреатикоеюностомия

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List of abbreviations

ASA — American Association of Anesthetists

CFTR — cystic fibrosis transmembrane conductance regulator (cystic fibrosis transmembrane regulator gene)

ERAS — early recovery after surgery

FTS — fast track surgery

Hb_{A1c} — glycosylated hemoglobin

IL-1 — interleukin-1

IL-6 — interleukin-6

IL-8 — interleukin-8

ISGPS — International Study Group for Pancreatic Surgery

SPINK1 — serine protease inhibitor, Kazal type 1 (pancreatic secretory inhibitor of trypsin)

TNF-α — tumor necrosis factor α

AIP — autoimmune pancreatitis

MPD — the main pancreatic duct

CI — Confidence Interval

BMI — body mass index

PPI — proton pump inhibitor

CIT — cystic-inflammatory transformation

CT — computed tomography

PA — pseudoaneurysm

ICD 10 — International Classification of Diseases 10 revision

MRI — magnetic resonance imaging,

MRCP — Magnetic Resonance Cholangiopancreatography

vf — field of view

PDR — pancreatoduodenal resection
P — pancreas
PF — pancreatic fistula
RGA — Russian Gastroenterological Association
RCT — Randomized Controlled Trial
ERCP — endoscopic retrograde cholangiopancreatography
DM — diabetes mellitus
TCBD — terminal section of the common bile duct
US — ultrasound examination
FPT — functional pancreatic tests
CP — chronic pancreatitis
ESMPD — endoscopic stenting of the main pancreatic duct
EUSPBA — endosonography of the pancreatobiliary area
PUD — peptic ulcer disease

Terms and definitions

Abscessing is the progression of the inflammatory process due to secondary infection that causes the formation of an abscess.

Pancreatic abscess is an infection localized in the tissues of the pancreas, filled with purulent and necrotic masses.

Virsungolite is a pancreatic duct stone.

Intraductal papillary mucinous tumor is a borderline malignant tumor of the pancreas, developing in its ductal system and characterized by the presence of papillary growths of the mucosa and the formation of mucin.

Cystic-inflammatory transformation (CIT) of the duodenum is an inflammatory and cystic lesion of its wall with localization in the descending part of the intestine, which occurs in patients with CP.

Pseudoaneurysm is a cavity that is located outside the vessel and communicates with its lumen. A pseudoaneurysm is formed when the vascular wall is damaged resulting in impaired integrity.

Pancreatic hypertension is an increase in pressure in the ductal system of the pancreas due to a violation of the outflow of pancreatic secretion, manifested by dilatation of the pancreatic duct.

Postnecrotic pancreatic cyst (pseudocyst) (Greek: κύστη — bubble) is a cavity that arose in the tissue of the pancreas as a result of necrosis of the parenchyma of the organ, containing pancreatic secretion and tissue detritus. True pancreatic cysts have an internal epithelial lining. The walls of pseudocysts lack such a lining and consist of fibrous tissue.

Steatorrhea or steatorrhea is a pathologic symptom characterized by the presence of an excessive amount of fat in the feces.

Functional tests of the pancreas are methods for determining the exocrine or endocrine pancreatic function.

Chronic pancreatitis is a long-term inflammatory disease of the pancreas, manifested by irreversible morphological changes that cause pain and/or a persistent decrease in function.

Exocrine pancreatic insufficiency is a clinical syndrome that occurs when more than 90 % of the active pancreatic parenchyma is destroyed.

Endoscopic papillosphincterotomy is a dissection of the sphincter apparatus of the major papilla of the duodenum using papillotome through duodenoscope.

Endoscopic retrograde cholangiopancreaticography is an endoscopic examination, which consists in the cannulation of the major papilla of the duodenum through a duodenoscope and the introduction of an X-ray contrast agent into the bile and pancreatic ducts under radiological control.

1. Brief information on a disease or condition (group of diseases or conditions)

1.1. Determination of a disease or condition (group of diseases or conditions)

Chronic pancreatitis (CP) is a long-term inflammatory disease of the pancreas, manifested by irreversible morphological changes in the parenchyma and ducts of the organ, which cause pain and/or a persistent decrease in function [1, 2].

1.2. Etiology and pathogenesis of a disease or condition (group of diseases or conditions)

Modern ideas about the etiology of CP are reflected in the classification TIGAR-O (toxic-metabolic, idiopathic, genetic, autoimmune, recurrent acute, obstructive) [3] according to which there are:

Toxic/metabolic
- Alcohol
- Tobacco smoking
- Hypertriglyceridemia
- Hypercalcemia
- Chronic renal failure
- Drug- or toxin-induced

Hereditary
- autosomal dominant:
  - cationic trypsinogen mutations (PRSS1)
- autosomal recessive:
  - CFTR mutations (cystic fibrosis transmembrane conductance regulator)
  - SPINK1 mutation (serine protease inhibitor, Kazal type 1)
  - cationic trypsinogen mutations

Autoimmune
- isolated AIP
- AIP associated with other autoimmune diseases

CP as a consequence of recurrent and severe acute pancreatitis
- postnecrotic (severe acute pancreatitis)
- recurrent acute pancreatitis

- vascular diseases / ischemic
- radiation

Obstructive

- stenosis of Oddi's sphincter
- obstruction of the duct (for example, tumor, periampulary cysts of the duodenum)
- post-traumatic scars of the pancreatic ducts (complication of endoscopic procedures: papillosphincterotomy, stone extraction, etc.)
- *pancreas divisum*

Idiopathic

- early onset (average age 20 years, pain)
- late onset (average age 56 years, no pain in 50 % of patients; rapid development of calcification, exo- and endocrine insufficiency)
- tropical:
  - tropical calcifying pancreatitis
  - fibrocalculous pancreatic diabetes.

Toxic factors

Alcohol is the cause of CP in 60–70 % of cases. The daily dose of alcohol intake at which CP occurs over a period of 10–15 years is approximately 60–80 ml/day. Sex, hereditary, and other factors may play a basic role, and as a result, the term "toxic pancreatitis" does not necessarily imply chronic alcoholism or the effects of alcohol abuse [4]. Smoking significantly potentiates the effect of alcohol (multiplicative effect), increasing the risk of development and also progression of CP [5, 6]. The results of observational studies indicate that the importance of tobacco smoking in the genesis of CP may be even more significant than that of alcohol [7].

Diet

The relationship between nutritional deficiency, the presence of any specific foods in the diet, as well as hypertriglyceridemia, other hyperlipidemia and the CP development has not been reliably established.

For the diagnosis of hypertriglyceridemic pancreatitis, it is necessary to increase serum triglycerides by more than 1000 mg/dL (11.2 mmol/L). However, a relapse of pancreatitis can occur already with a smaller rise in the level of blood triglycerides — more than 500 mg/dL (5.6 mmol/L) [8, 9].

Hereditary factors

Mutations in the cationic trypsinogen gene (PRSS1) lead to the synthesis of pathologically active trypsin and the development of hereditary pancreatitis [10] In patients with hereditary pancreatitis, symptoms usually occur much earlier (before the age of 20), the disease progresses rapidly, against this background, the risk of developing pancreatic adenocarcinoma increases.

In patients with idiopathic CP, mutations of the cystic fibrosis transmembrane conduction regulator (CFTR) gene [11] and the trypsin inhibitor (PSTI or SPINK1) [12]. In the general Russian population, the N34S mutation in the SPINK1 gene is significantly more common than in the control (14.6 and 2.9 %, respectively; $p < 0.05$). The ratio of the chances of developing idiopathic CP in the presence of the N34S mutation in this study was 4.6 [13]. The N34S mutation is detected in over 10 % of idiopathic CP cases [14].

Duct obstruction

Conditions associated with the development of obstructive CP are trauma, the presence of stones, pseudocysts and tumors. It is not conclusively proven whether CP occurs against the background of pancreas divisum and dysfunction of the sphincter of Oddi.

Immunological factors

AIP can occur in isolation or in combination with Sjögren's syndrome, inflammatory bowel disease, and many other autoimmune diseases [15]. In recent years, two types of AIP have been identified [16].

Other and rare metabolic factors

Proven causes of CP include chronic renal failure and hyperparathyroidism, ischemic lesions in atherosclerosis of the mesenteric vessels, while the exact role of drugs and toxic substances remains unproven [17]

Cystic-inflammatory transformation (CIT) of the duodenum is an inflammatory and cystic lesion of its wall with localization in the descending duodenal part, which occurs in patients with CP. Three mechanisms for the development of CIT are possible:

1. Inflammation of the dorsal part of the pancreatic head, embedded in the wall of the duodenum, due to obstructed outflow of secretion through the Santorini duct.
2. Secondary spread of the inflammatory process from the pancreatic head to the paraduodenal tissue and the wall of the duodenum.
3. Rarely — a primary cystic-inflammatory lesion of true heterotopic pancreatic tissue with secondary obstructive pancreatitis or with accompanying toxic CP development in alcohol abuse [18].

1.3. Epidemiology of disease or condition (group of diseases or conditions)

The prevalence of CP in Europe is 25.0–26.4 cases per 100 thousand population, in Russia — 27.4–50.0 cases per 100 thousand population [17]. The incidence of CP in developed countries ranges from 5–10 cases per 100 thousand population; in the world as a whole — 1.6–23.0 cases per 100,000

population per year [19–22]. In the world, there is a tendency to increase the incidence of acute and chronic pancreatitis, over the past 30 years — over 2-fold [17]. Usually CP develops in adulthood (35–50 years). In developed countries, the average age since diagnosis has decreased from 50 to 39 years, males develop CP 2 times more often than females, there is a tendency to increase the proportion of women among the CP patients (by 30 %); primary disability of patients reaches 15 % [8, 21].

Mortality after the initial diagnosis of CP is up to 20 % during the first 10 years, and more than 50 % — after 20 years, averaging 11.9 %. 15–20 % of patients with CP die from complications that occur during exacerbations of pancreatitis, others — due to secondary disorders of digestion and infectious complications [19, 20].

1.4. Encoding of disease or condition (group of diseases or conditions) according to the International Classification of Diseases and Related Health Problems

K.86.0 Alcoholic chronic pancreatitis

K.86.1 Other forms of chronic pancreatitis (infectious, continuously recurrent, recurrent)

K.86.2 Pancreatic cyst

K.86.3 Pancreatic pseudocysts

K.86.8 Other specified diseases of the pancreas (atrophy, lithiasis, fibrosis, cirrhosis, pancreatic infantilism, necrosis)

K.90.1 Pancreatic steatorrhea

1.5. Classification of disease or condition (group of diseases or conditions)

1. By etiology:
- Biliary-dependent
- Alcoholic
- Dysmetabolic
- Infectious
- Drug-induced
- Autoimmune
- Idiopathic

2. By clinical manifestations:
- Painful
- Dyspeptic
- Combined
- Latent

3. According to morphological signs:
- Interstitial-edematous
- Parenchymal
- Fibrous-sclerotic
- Hyperplastic
- Cystic

4. By the nature of the clinical course:
- Rarely recurrent
- Frequently recurring
- With persistently present symptoms of CP

5. Complications:
- Obstruction of the outflow of bile and the passage of duodenal contents
- Portal hypertension (subhepatic)
- Pseudoaneurysm
- Endocrine disorders:
  - pancreatic diabetes mellitus,
  - hypoglycemic conditions, etc.
- Inflammatory changes: abscess, cyst, parapancreatitis, «enzymatic» cholecystitis, pneumonia, exudative pleurisy, paranephritis, etc.

1.6. Clinical picture of a disease or condition (group of diseases or conditions)

The most typical clinical manifestations of CP are abdominal pain and symptoms of pancreatic insufficiency, but in some cases, the clinical presentation of the disease can manifest by signs of complications.

Abdominal pain is the main symptom of CP. Usually, the pain is localized in the epigastrium with irradiation in the back, intensifying after meals and decreasing in a sitting position or leaning forward. Pain is observed in 80–90 % of patients, in 10–20 % there is "painless pancreatitis" [23]. Attacks of pain can recur (type A: short attacks of pain lasting up to 10 days against the background of long painless periods), sometimes patients experience persistent pain (type B: more severe and prolonged pain episodes with painless periods lasting 1–2 months, more often observed in alcoholic CP) [24].

Symptomatic ***exocrine*** pancreatic ***insufficiency*** occurs only with a decrease in the functional activity of the gland by more than 90 %. Clinical manifestations of malabsorption of fats are steatorrhea and flatulence, weight loss (in 30–52 % of patients). Alcoholic pancreatitis more often than pancreatitis of another etiology leads to exocrine insufficiency [25] In patients with alcoholic pancreatitis, signs of maldigestion occur on average 10 years after the appearance of the first clinical symptoms.

Endocrine pancreatic insufficiency develops over time in 70 % of patients with CP in the form of impaired glucose tolerance. Diabetes mellitus occurs with a long course of CP, the risk of diabetes mellitus gradually increases with 10 years from the beginning of CP [26, 27].

Pancreatogenic diabetes differs from type 1 and type 2 diabetes by a higher risk of hypoglycemia and a lower incidence of ketoacidosis [28, 29]. To date, pancreatic diabetes mellitus in the outcome of the CP development should be attributed as the type 3c [29].

Complications such as macro/microangiopathy, nephropathy, neuropathy, and retinopathy are as common as in type 1 diabetes [30].

The clinical manifestations of the disease vary significantly depending on its stage [31] (Table 1).

Table 1. Determination of the clinical stage of CP with prognosis assessment

Stage	Signs	Prognosis
1	Preclinical. Radiological signs of CP	Unknown
2	Initial manifestations. Type "A" pain. Repeated attacks of acute pancreatitis. Decreased quality of life. Duration: 4–7 years	Increased risk of pancreatic necrosis, complications of acute pancreatitis
3	Persistent symptoms. Endo- and/or exocrine insufficiency	Nutritional failure
4	Atrophy of the pancreas. Severe pancreatic insufficiency. The intensity of pain decreases, there are no episodes of acute pancreatitis	Diabetes mellitus, nutritional failure. Increased risk of pancreatic cancer

Complications of chronic pancreatitis

Approximately 1/3 of patients with CP have *pancreatic pseudocysts* [32] they can be of a wide variety of sizes, more often asymptomatic, or cause signs of compression of neighboring organs, causing pain in the upper half of the abdomen. Spontaneous regression of pseudocysts in CP occurs less often than in acute pancreatitis [32]; in patients with alcoholic CP, spontaneous regression is described in 25.7 % of cases, and persistence without clinical manifestations in 23 % [33]. The risk of severe complications in the asymptomatic chronic pseudocysts is <10 % [32].

Relapse of CP and repeated attacks of acute pancreatitis at the background of CP can lead to *pancreatic necrosis with the development of infectious complications* (inflammatory infiltrates, abscesses, purulent cholangitis, septic conditions). *Duodenal stenosis* develops in less than 5 % of the cases. The main cause of duodenal obstruction is the involvement of paraduodenal fat tissue and the duodenal wall to inflammatory process. The development of a decompensated stomach obstruction is rare [34–36].

Edema and the development of pancreatic fibrosis can cause compression of the common bile duct with the development *of obstructive jaundice* (in 16–35 % of patients). In some cases, jaundice can be permanent or recurrent, with a low risk of secondary biliary liver cirrhosis. The jaundice is preceded by upper abdominal pain, typical for CP relapse [22, 37, 38].

Portal hypertension caused by compression or thrombosis of the portal, superior mesenteric or splenic veins due to inflammation and fibrosis of the peripancreatic tissue is noted in 7–18 % of patients. Bleeding from esophageal or stomach varicose veins is not a common complication of CP [39].

Intestinal bleeding in patients with CP is a pathognomonic symptom of a *pseudoaneurysm (PA) of the branches of the celiac trunk and the superior mesenteric artery*. At the same time, gastroduodenoscopy does not detect stomach and duodenum ulcers, esophageal varices. Hemorrhage from the main duodenal papilla during duodenoscopy is recorded in 14 % of cases.

The consequence of progressive pancreatic fibrosis and pancreatic maldigestion, not controlled by enzyme replacement therapy, is malabsorption syndrome with the development of micronutrient deficiency. Therefore, signs of deficiency of essential macro- and micronutrients are also attributed to complications of CP with exocrine pancreatic insufficiency [40, 41]. Patients with CP are primarily at risk of vitamin A, D, E and K [42, 43] and vitamin B_{12} deficiency. Osteoporosis is an common complication of CP [41].

With a long course of CP, the risk of pancreatic cancer increases [44, 45]. For patients with a five-year history of CP, the risk of cancer increases 8 times [46] According to the meta-analysis, with a moderate risk of developing pancreatic cancer (OR 1.41; 95 % CI 1.07–1.84; $p = 0.013$) associated CFTR gene mutations in CP, and SPINK1 gene mutations do not increase cancer risk (OR 1.52; 95 % CI, 0.67–3.45; $p = 0.315$) [14]. Pancreatic intraepithelial neoplasia (PanIN) – specific morphological changes in the ductal epithelium [17].

Possible complications also include: *erosive esophagitis, Mallory-Weiss syndrome, gastroduodenal ulcers (they are caused by a significant decrease in the production of pancreatic bicarbonates), and abdominal ischemic syndrome.*

2. Diagnosis of disease or condition (group of diseases or conditions), medical indications and contraindications for diagnostic methods

Criteria for establishing the diagnosis of the disease / condition

The diagnosis of chronic pancreatitis is established on the basis of:

1) past history (characteristic complaints of attacks of abdominal pain and/or clinical signs of

exocrine and/or endocrine insufficiency of *the pancreas, detection of chronic pancreatitis before),*

2) physical examination (palpatory painfullness of the abdominal wall in the projection of the pancreas),

3) laboratory examination (signs of exocrine and endocrine insufficiency of the pancreas according to functional tests),

4) instrumental tests (calcifications in the parenchyma and pancreatic duct stones, dilatation of the main pancreatic duct and its branches according to CT, MRCP, EUS).

Comments: *It is recommended that the diagnosis of CP be established on the basis of reliable morphological criteria or a combination of morphological and functional criteria. CT, as well as MRCP and EUS, are recommended as the methods of choice for verifying the diagnosis of CP. To verify the diagnosis, it may be necessary to perform one or all of the most accurate methods, including dynamic examination after 6-12 months if the detectable signs do not correspond sufficiently to the diagnosis of CP.*

2.1. Symptoms and anamnesis

Complaints and history data characteristic of patients with CP are indicated in subsection 1.6.

2.2. Physical examination

Physical examination during the period of exacerbation of CP allows you to determine the painfullness in the Chauffard area at abdominal palpation, combined with moderate abdominal resistance; positive Mayo-Robson sign is pain at palpation in the region of the left costovertebral angle.

2.3. Laboratory tests

Determination of the activity of alpha-amylase, lipase in the blood serum is not a diagnostic marker of CP, but its determination is recommended for patients with CP on the first day of hospitalization and further in dynamics during one hospitalization for the diagnosis of complications and recurrence of acute pancreatitis on the background of CP [47–49].

Grade of Recommendation: B. Evidence level: 2.

Comments: *The level of amylase and blood lipase in CP may be slightly increased, within normal values or below normal values, which is explained by the focal inflammatory process and the severity of pancreatic fibrosis; in contrast to acute pancreatitis, which is almost always characterized by an increase in enzyme levels in the blood and urine. In the case of elevated amylase in CP, the formation of a pseudocyst or pancreatic ascites can be suspected. Persistently serum amylase elevation suggest macroamylasemia (with amylase forming large complexes with plasma proteins that cannot be filtered into primary urine, and urine amylase activity is normal) or extrapancreatic sources of hyperamylasemia (renal failure; diseases of the salivary glands (mumps, stones, radiation sialadenitis); complications of maxillofacial surgery; "neoplastic" hyperamylasemia (lung cancer, esophageal cancer, ovarian cancer); burns; diabetic ketoacidosis; pregnancy; kidney transplantation; brain injury; the use of drugs (morphine); diseases of the biliary tract (cholecystitis, choledocholithiasis), complications of peptic ulcer disease — perforation or penetration of ulcers, obstruction or infarction of the intestine, ectopic pregnancy, peritonitis, aortic aneurysm, postoperative hyperamylasemia)*

· For the diagnosis **of exocrine pancreatic insufficiency** in clinical practice in patients with CP, it is recommended to determine the activity of pancreatic elastase-1 in stool [50–52].

Grade of Recommendation: A. Evidence level: 2.

Comments: *Direct methods*

Classical tube methods for determining the volume of pancreatic juice, assessment of enzyme and bicarbonate concentrations in it have extremely limited application for the diagnosis of CP due to invasiveness, high cost, low availability of stimulators (to date, substances are not registered for medical use in the Russian Federation), laboriousness and poor patient tolerance. According to these methods, it is impossible to distinguish CP from the insufficiency of the pancreatic function without CP. Direct methods can only be used in clinical trials in highly specialized clinics. In some complex cases, the technique is applicable for the differential diagnosis of steatorrhea.

The improvement of the pancreatobiliary EUS technique *with secretin stimulation allows, in addition to examining pancreatic ducts, to carry out a time-based evacuation of duodenal contents after the secretin stimulation, thus reproducing the classic secretin test by endoscopy. The limitation of the method is a lack of experience and validation, which is reflected in the absence of this method in all foreign national recommendations for the diagnosis of pancreatic insufficiency today. In Russia, the main restriction for its use is the unregistered secretin.*

Indirect methods

Indirect FPT indirectly assess the impairment of exocrine function, they are more accessible than direct methods, but have less sensitivity and mainly detect late stages of exocrine insufficiency.

A standard general stool test with microscopy of neutral fat droplets has low sensitivity, therefore, using it to verify the steatorrhea and assess the effectiveness of treatment, it is necessary to repeat test 3 times and take into account the patient's diet.

The quantitative stool fat content determination method was developed in 1949, it is sensitive to the

diagnosis of pancreatic function deficiency in the later stages [17]. The test is carried out after the keeping high-fat diet for 5 days at the absence of enzyme replacement therapy, the collection of feces is carried out within 72 hours. Normally, the fat absorption rate is at least 92 % [53]. The method of quantitative evaluation of the fat content in the feces is used mainly in clinical trials, in routine clinical practice it is difficult to apply.

Determination of the activity of elastase-1 in the feces. Elastase-1 maintains relative stability compared to other enzymes of the pancreas at the passage through the gastrointestinal tract. The greatest benefit is the determination of elastase in the feces by the enzyme immunoassay method (using monoclonal antibodies) as only human elastase is detected, so the test results do not depend on replacement therapy. The study is non-invasive and relatively inexpensive, but has a low sensitivity in mild to moderate exocrine pancreatic insufficiency, and low specificity in a certain gastrointestinal pathology not associated to the pancreas [54]. In mild exocrine insufficiency, the sensitivity of the method is 63 %.

The diagnostic accuracy of the fecal elastase test is significantly reduced by rapid transit, diarrhea, polyfecaly, leading to false positive results (low elastase activity) due to the dilution of the enzyme; a similar problem can occur with small intestinal bacterial overgrowth due to bacterial hydrolysis of elastase. The degree of exocrine pancreatic insufficiency can be assessed after stopping/minimizing the main symptoms of exocrine pancreatic insufficiency (diarrhea, steatorrhea) at the initial therapy with encapsulated enzyme preparations [68].

Decreased activity of elastase in stool indicates primary exocrine pancreatic insufficiency (severe: 0–100 ug/g; medium or mild: 101–200), which is most often indication for lifelong high-dose enzyme replacement therapy. It practically makes no use for repeated testing of elastase activity, because the number of remaining, functionally active secreting pancreatic cells cannot increase. Determination of elastase-1 activity in feces is recommended for the diagnosis of CP with equivocal results of imaging methods, when exocrine pancreatic insufficiency will serve as an indirect sign of CP.

Breath test. The oral breath test consists of administration of ^{13}C-labeled substrate (mixed triglycerides), which is hydrolyzed in the lumen of the intestine to a degree proportional to the activity of pancreatic lipase. Exhaled $^{13}CO_2$ is determined by mass spectrometry or infrared spectroscopy, but, as with other indirect tests, this analysis has variable sensitivity and specificity, depending on a large number of factors. In addition, we can observe contradictory results in recent years. It should be recognized that the improvement and unification of this technique, the use of standard validated equipment, strict adherence to the test methodology all together open up broad prospects for its widespread use [53]. The lack of a substrate approved for use in Russia (^{13}C-mixed triglycerides) makes the test unavailable at present time.

· All patients with CP in order to assess **endocrine insufficiency of** the pancreas are recommended to undergo regular (at least once per year) study of glycosylated hemoglobin level, fasting blood glucose levels or a glucose tolerance test [27].

Grade of Recommendation: B. Evidence level: 2.

Comments: *Diagnosis of endocrine insufficiency should be timely and thorough by regularly (at least 1 time per year)* examination of glycosylated hemoglobin, fasting blood glucose levels or glucose tolerance test. *The optimal form of screening remains controversial [28]. The international expert committee recommended the use of Hb_{A1c} (at ≥6.5 %), rather than blood glucose concentration for diabetes diagnosis [55].*

2.4. Instrumental diagnostic studies

The choice of imaging technique should be based on its availability, availability of appropriate experience of the staff and the degree of invasiveness of the method.

· All patients with clinical symptoms typical for CP, at the initial visit to doctors of any profile, should undergo specific examination using radiological diagnostic methods to confirm or exclude CP [38, 56, 57].

Grade of Recommendation: C. Evidence level: 5.

Comments: *The characteristic clinical picture, abnormal results of functional tests of the pancreas, allows the clinician to consider the diagnosis of CP as possible or uncertain (i.e. clinical suspicion of CP), which requires the use of more accurate radiological methods to confirm the diagnosis.*

Plain abdominal radiography allows you to identify only severe calcification in the projection of the pancreas. This method is obsolete. According to the results of the studies, plain radiography in 30–40 % of cases allows to detect calcification of the pancreas or intraductal stones, especially at oblique projection. Formally, such a finding previously excluded the need for further examination to confirm the diagnosis of chronic pancreatitis [58]. At the same time, pancreatic calcification is most often found in alcoholic, hereditary CP and rarely — in idiopathic pancreatitis [17]. Moreover, calcification may be also seen in pancreatic neoplasms, which, in combination with low sensitivity, does not allow us to recommend

this technique as competitive and having diagnostic value.

• Transabdominal ultrasound is recommended for the primary screening of patients with clinical symptoms typical of CP, to exclude other causes of abdominal pain due to the non-invasiveness of the method, easy accessibility, sufficient specificity in determining the main manifestations of CP — enlargement of the pancreas, the presence of pancreatic duct dilation, pancreatic duct stones and calcification of the parenchyma, postnecrotic cysts [38, 56, 57].

Grade of Recommendation: C. Evidence level: 5.

Comments: *Transabdominal ultrasound acts as a primary screening method for unexplained abdominal pain. This method allows to identify free fluid in the abdominal cavity, assess the changes of the liver, biliary tract, kidneys, the pathology of which can mimic or accompany CP, in some cases — to exclude surgical and gynecological diseases.*

Ultrasound has low sensitivity and specificity in the diagnosis of CP. Even in specially designed studies with a high-level specialists and equipment used, the absence of restrictions in the duration of the procedure, a standardized approach to the study and high inter-observer consistency, the sensitivity and specificity of transabdominal ultrasound do not exceed 70–80 %, which is definitely insufficient for the diagnosis of CP [59].

The study should include an examination of all organs of the abdominal cavity, retroperitoneal space and small pelvis. Characteristic ultrasound signs of CP, detected in the B-mode, are an increase in the echogenicity of the parenchyma, the heterogeneity of the structure due to multiple hyperechoic stranding — fibrosis sites, the presence of parenchymal calcifications and stones in pancreatic ducts, the diameter of the PD over 2 mm, postnecrotic cysts. Diffuse changes of pancreatic parenchyma properties and increase in its size without above mentioned changes do not allow to establish the presence of CP [60]. Transabdominal ultrasound is able to confirm the diagnosis of CP at the late stage, to detect calcification of the pancreas and intraductal calcium stones (if their size exceeds 5 mm), pseudocysts, dilatation of the MPD and its lateral branches, atrophy of the pancreatic parenchyma [28, 61].

• Monitoring by transabdominal ultrasound is recommended for CP patients with asymptomatic pancreatic pseudocysts in order to diagnose possible complications in time *[28, 61].*

Grade of Recommendation: C. Evidence level: 5.

Comments: *High sensitivity to fluid collections makes ultrasound a method of choice for monitoring of patients with pancreatic pseudocysts.*

• In the absence of CP signs at transabdominal ultrasound, it is recommended to continue the investigation, to perform other instrumental studies — endosonography of the pancreatobiliary area (EUSPBA) and abdominal CT with intravenous bolus enhancement [62]

Grade of Recommendation: 5. Evidence level: C.

Comments: *To date, it can be argued that transabdominal ultrasound is not able to detect CP in the early stages [62] significantly inferior to CT and* EUSPBA *images, spatial and contrast resolution. Thus, a negative ultrasound result does not exclude even the presence of pancreatic stones. The term "diffuse pancreatic changes" according to ultrasound conclusion should not result in the diagnosis of chronic pancreatitis.*

• Abdominal computed tomography with intravenous bolus enhancement (with the obligatory recording the native, arterial, venous and delayed phases images) is the method of choice in the diagnosis of CP and is recommended to all patients in order to identify specific changes in the pancreas, including pancreatic necrosis. CT is recommended for all patients with suspected CP, no later than 2 weeks from the date of initial visit [28]. This recommendation is intended for the 3rd level medical institutions.

Table 2. Changes in the pancreas in CP according to radiological diagnostic methods

Feature	Changes
Organ size	Usually — enlargement of the part or the whole organ, rarely — decrease in the size of the pancreas
Tissue density	As a rule, it is increased, non-homogeneous, usually with cysts or calcification.
Contour	Uneven
Main duct	Dilated (diagnosis by CT is possible if the diameter of the duct > 5 mm)
Bile ducts	Dilated at enlarged pancreatic head
Duodenum	Compressed at enlarged pancreatic head
Splenic vein	Sometimes thrombosed, in sometimes -- with enlarged spleen
Other signs	Thickening of the peritoneum and renal fascia near the pancreas. Retroperitoneal fat tissue atrophy

Grade of Recommendation: C. Evidence level: 5.

Comments: *Abdominal CT with intravenous bolus enhancement is the method of choice for the primary diagnosis of CP, significantly superior in diagnostic value to transabdominal ultrasound and is more available in Russia today then EUS and secretin-stimulated magnetic resonance cholangiopancreatography (sMRCP). For the effective use of all the possibilities of CT, reliable diagnosis of edema, necrosis, pancreatic tumors, it is of great importance to perform a study with intravenous bolus enhancement and scanning of all phases of contrast research. The native phase of the computer tomogram is necessary for the detection of pancreatic stones, arterial — for visualization of* pseudoaneurysms *of splenic, gastroduodenal artery, venous — for differential diagnosis with other diseases of the pancreas (IPMN 2 type), delayed — to determine the degree of fibrous changes in the pancreatic parenchyma.*

CT with intravenous contrast allows you to detect areas of pancreatic necrosis (no accumulation of contrast agent). The sensitivity of the method in the diagnosis of CP is 75–90 % specificity — 85–90 % [28]. With exacerbation of CP, CT with intravenous contrast is able to confirm the diagnosis, assess the severity of the exacerbation and identify the presence of complications. The Cambridge classification of the severity of CP according to CT and ultrasound data is presented in Appendix G4 (Table 4).

• Abdominal computer tomography with intravenous bolus enhancement is recommended as the most effective method for determining the localization of stones and intraductal stones of the pancreas, as well as for the differential diagnosis of CP and pancreatic tumors over 5 mm in size in patients with CP. The absence of changes in the pancreas at CT does not exclude the presence of early stage CP, however, this probability is significantly lower regarding the use of transabdominal ultrasound [57, 59].

Grade of Recommendation: C. Evidence level: 5.

Comments: *CT data indicative of CP are pancreatic atrophy, presence of ductal stones, dilation of MPD, intra- or peripancreatic cysts, thickening of peripancreatic fascia, and thrombosis of the splenic vein [63]. CT scan can reveal signs indicative of probable CP: heterogeneity of the parenchyma, fuzziness of contours, and enlargement of the pancreas [64].*

• In patients with recurrent abdominal pain with negative CT results, endoscopic ultrasonography (EUS) is recommended for the differential diagnosis of CP and other inflammatory and neoplastic diseases of the pancreas [65–68].

Grade of Recommendation: C. Evidence level: 4.

Comments: *Endoscopic ultrasonography is the most sensitive method for detecting CP at an early stage [65, 66] EUS is a minimally invasive imaging technique that is also used for therapeutic purposes [61] The severity of CP is assessed according to the classification adopted in 2007 (Rosemont classification) [65, 66] Rosemont's criteria include: 6 parenchymal signs reflecting the state of the organ parenchyma, which are divided into large (A, B) and small (Appendix G2): hyperechogenic foci with shadowing, lobularity with "honeycombing", lobularity without the "honeycombing" sign, hyperechoic foci without shadow, hyperechoic cords, cysts and 5 ductal criteria, which are also divided into large and small signs: the presence of stones, dilation of the MPD, expansion of the lateral branches, irregularity of the main duct, hyperechoic duct walls. There are 4 groups of signs according to the reliability of the diagnosis of CP: definite, presumptive, uncertain and normal. The use of elastography and/or contrast during EUS can increase the sensitivity of the method in the detection of CP and differential diagnosis with tumors [69].*

Differential diagnosis between inflammatory and malignant changes, as well as early detection of malignancy in patients diagnosed with CP, remains a difficult task for all imaging techniques, but the method that gives the most accurate tissue characterization is EUS with fine-needle biopsy [70].

Under endosonographic control, a diagnostic needle biopsy can be performed for cytological and histological verification of suspicious areas for differential diagnosis of CP, autoimmune pancreatitis and neoplasms [65–67].

• EUS is recommended for patients with suspected or diagnosed CP as the most informative method in the diagnosis of early CP (CP of minimal changes), especially with secretin stimulation, contrast enhancement and elastography of the pancreas, however, this method requires highly qualified specialist and a strictly standardized approach (79, 82, 84).

Grade of Recommendation: C. Evidence level: 3.

Comments: *Pancreatobiliary EUS, as well as secretin-stimulated MRCP, are the most reliable methods for visualizing changes in the parenchyma and ducts of the pancreas in the early stages of CP, as well as ductal abnormalities [61, 71].*

• Endoscopic endosonography of the pancreatobiliary zone is recommended for patients with suspected obstructive etiology of pancreatitis (clinical or radiological signs of pancreatic or biliary hypertension, endoscopic signs of changes in the major duodenal papilla) [66, 69, 70]. This recommendation is intended for 3rd level medical organizations.

Grade of Recommendation: C. Evidence level: 3.

• For patients with intolerance to iodine-containing contrast agents are recommended to perform MRI in order to detect CP and differential diagnosis of the causes of biliary and pancreatic hypertension. MRI data indicating CP are local or diffuse changes in signal intensity on T1-WI and T2-WI, including fat-suppressing signal, reducing contrast in the arterial and venous phases with dynamic MRI and increasing contrast in delayed phase due to contrast of fibrous tissue [72–75].

Grade of Recommendation: B. Evidence level: 2.

Comments: *MRI is preferable in patients with intolerance to iodine-containing contrast agents. MRI data indicating CP include decrease in the intensity of the signal at T1 and T2-WI in fat-suppressing mode and decrease in contrast enhancement. At magnetic resonance cholangiopancreatography (MRCP) it is possible to determine fluid-containing lesions with high accuracy — pancreatic duct and pseudocysts. The presence of fluid inside the pseudocyst is a natural contrast, which makes it possible to detect it both in standard MRI and in MRCP. In the T2 and T2-STIR mode, cysts have homogeneous hyperintense MR signal, clear smooth contours. MRI makes it possible to distinguish the hemorrhagic component of the fluid, which is determined as a hyperintense MR signal in T1-FFE-WI, which is explained by the significant paramagnetic effect of methemoglobin [68, 72–76].*

• MRCP is the most informative in the differential diagnosis of the causes of biliary and pancreatic hypertension and is recommended for patients with CP in order to clarify changes in the ductal system [77].

Grade of Recommendation: A. Evidence level: 2.

Comments: *Since the lateral branches are visualized only in 10–25 % of cases [68, 72–75], this study has limited diagnostic value in the early stages of CP. The disadvantage of MRI is that in the presence of calcifications (which is typical for CP), this method cannot have such a high specificity as CT. However, the presence of areas of very low signal intensity suggests the presence of calcified zones, indicative of inflammatory process [74, 75, 78] and may be valuable for a small group of patients in whom other diagnostic methods do not allow to confirm the alleged diagnosis of CP.*

• MRCP and pancreatobiliary EUS with secretin stimulation are recommended as the best imaging methods for diagnosing changes in the parenchyma and ducts in patients with CP in the early stages. Dynamic MRCP with a secretin test is recommended as the main non-invasive method of identifying initial morphological changes in the pancreatic duct system, cystic lesions, as well as for evaluation of exocrine reserve of the pancreas [79, 80]. This recommendation is intended for 3rd level medical organizations.

Grade of recommendations B. Evidence level 3.

Comments: *The combination of MRI and MRCP with secretin stimulation is the most accurate method of verifying pancreatitis of minimal changes. The use of contrast significantly increases the sensitivity of the method in the differential diagnosis of CP and pancreatic tumors. When performing MRCP, fluid-filled structures can be determined with high accuracy: MPD and pseudocysts [79, 80].*

• MRCP and EUSPBA are recommended as the most accurate methods for diagnosing pancreatic abnormalities in patients with CP [79].

Grade of Recommendation: C. Evidence level: 5.

Comments: *Secretin-stimulated MRCP has high sensitivity [79] and may be valuable in a small group of patients with initial stages of ductal changes in CP, precancerous conditions (PanIN, intraductal papillary neoplasia), and pancreatic adenocarcinoma.*

• Retrograde cholangiopancreatography (ERCP) is not recommended as a method for diagnosing CP because of the risk of serious complications (acute pancreatitis, cholangitis, sepsis, retroduodenal perforation). ERCP in patients with CP is recommended to be considered as a component of therapeutic endoscopic intervention (for example, stenting of MPD at relapse or external fistula), and not only diagnostics [68, 76].

Grade of Recommendation: C. Evidence level: 5.

Comments: *ERCP is invasive procedure with* a *high risk of serious complications, allows you to assess the state of pancreatic duct and its branches in detail (irregular dilation of the ducts — the "chain of lakes"), pseudocysts, reliably establish the diagnosis of CP. It can be most valuable in the absence of ERCP or dubious results of MRCP. The disadvantage of the method is the inability to assess the state of the pancreatic parenchyma. However, this technique in chronic pancreatitis should not be performed only for diagnostic purposes. The criteria for assessing the pancreatograms of CP from* the *ERCP and MRCP data are given in Appendix G3, Table 3.*

2.5. Other diagnostic studies

• The study of the level of serum IgG_4 is recommended for patients with suspected autoimmune pancreatitis and with differential diagnosis with pancreatic cancer [81–83]. This recommendation is intended for 3rd level medical organizations.

Grade of Recommendation: A. Level of reliability of evidence 1.

Comments: *Meta-analyses show high specificity and relatively low sensitivity of increased IgG_4 and IgG* levels *in the diagnosis of autoimmune pancreatitis and the differential diagnosis of focal tumor-like pancreatitis with pancreatic cancer. Clinically significant serum indicators for the diagnosis of AIP, differential diagnosis with pancreatic cancer include hypergammaglobulinemia, increased IgG levels, increased serum IgG_4 levels [81, 82] and the presence of antinuclear antibodies to Sm antigen. Timely detection of this condition is important,* since it *responds well to treatment with systemic corticosteroids.*

• Nutritional status assessment using clinical and biochemical methods is recommended for all patients with CP upon admission to the hospital, as well as on outpatient treatment, to assess the severity of the course of CP and predict the risk of complications and adverse outcomes [84, 85].

Grade of Recommendation: C. Evidence level: 4.

Comments: *The assessment is based on the calculation of the body mass index (BMI), evaluation of weight loss and its severity, the presence of indirect signs of nutritional failure during the physical examination — signs of anemia, trophic skin disorders, signs of kwashiorkor, etc. [84, 85]. The criteria for the clinical assessment of trophological status are given in Appendix G6.*

Laboratory assessment of nutritional status is for most Russian clinics generally available and indicative even when using a combination of simple tests — determination of total protein, albumin, absolute count of peripheral blood lymphocytes, hemoglobin level. The expansion of the spectrum of biochemical markers of nutritional failure to the determination of the concentrations of retinol-binding protein, vitamin B_{12}, folic acid, transferrin, magnesium, zinc allows you to assess in detail the nutritional status of CP patient [41].

Since 90 % or more of patients with CP with various markers of nutritional failure have a loss of body weight [84] the practitioner needs to know that even patients with a normal or elevated BMI often develop nutritional failure, and weight loss is the most significant potential marker of the risk of developing nutritional failure.

• Patients with CP are encouraged to perform a one-time bone mineral density assessment (X-ray densitometry) for the early diagnosis of osteoporosis that develops with exocrine pancreatic insufficiency and vitamin D malabsorption [28, 61].

Grade of recommendations — C. Evidence level: 5.

Comments: *Osteoporosis is a proven complication of CP resulting from pancreatic malabsorption, including in the absence of obvious signs of exocrine pancreatic insufficiency [40].*

3. Treatment, including drug and non-drug therapy, diet therapy, anesthesia, medical indications and contraindications to the use of treatment methods

3.1. Diet therapy

• All patients with CP are advised to completely stop drinking alcohol in order to reduce the incidence of severe complications and mortality *[7, 33, 61, 86–89].*

Grade of Recommendation: C. Evidence level: 4.

Comments: *In conditions of abstinence, in some cases, there has been a decrease in the severity of symptoms and pain relief, while continued alcohol intake contributes to the progression of the disease [7, 33, 61, 86–89]. Exocrine pancreatic insufficiency, as a rule, does not progress at the background of alcohol abstinence [86]; the patients who abstain from alcohol have a better response to analgesics [24, 45, 86, 87, 90–92]. However, the refusal to drink alcohol does not always stop the progression of the disease. To stop alcohol use, it is necessary to involve narcologists-psychiatrists specializing in alcohol dependencies followed by a psychologist [28].*

• All patients with CP are advised to quit smoking to reduce/relieve pain and prevent complications of CP [92, 93].

Grade of Recommendation: C. Evidence level: 4.

Comments: *Regardless of the course of CP, patients are advised to quit smoking as a significant and independent factor in the CP development [92, 93]. In general, it is very difficult to evaluate the independent role of smoking with concomitant alcohol abuse, as an etiological factor and a modifying factor affecting the course of CP, since smoking and* alcohol *abuse are often combined [7, 89, 94].*

• Patients with CP are recommended to take frequent small-volume meals with a high content of proteins and carbohydrates in order to improve the absorption of nutrients and make up for nutrient deficiencies. The degree of fat restriction depends on the severity of malabsorption and the efficacy of enzyme replacement therapy [108].

Grade of Recommendation: C. Evidence level: 5.

Comments: *Frequent small-volume meals are recommended: in small portions 5–6 times per day, depending on the severity of the disease [95]. It is*

desirable to have a high content of protein and carbohydrates in meals, if this does not increase pain and dyspeptic symptoms. The degree of fat restriction in exocrine pancreatic insufficiency depends on the severity of steatorrhea, in most cases intake of fats should not be restricted, especially — unrefined vegetable fats.

• Patients with severe exocrine pancreatic insufficiency, who at adequate replacement therapy, still experience severe steatorrhea, causing severe discomfort leading to social maladaptation, should keep a diet containing less than 40–60 g of fat per day [84, 85, 96].

Grade of Recommendation: C. Evidence level: 5.

Comments: *Protein-energy deficiency is common in patients with CP and is multifactorial in nature, due to the restriction of the amount of taken food, malabsorption, diabetes, impaired intestinal peristalsis and concomitant chronic alcohol intake [84, 85, 96]. Indicative recommendations for patients with severe exocrine pancreatic deficiency include a diet with daily energy value of 2,500 to 3,000 calories, and a intake of protein 1.0 to 1.5 g/kg/day [96]. Resolution of steatorrhea should be achieved not by limiting of fat intake (which is required for normal fat-soluble vitamin absorption (A, D, E and K), but by prescribing enzyme replacement therapy in an adequate dose.*

Complex carbohydrates and dietary fiber can be useful for slowing the development of diabetes, preventing the small intestinal bacteria overgrowth syndrome. Dietary fiber intake is often restricted in patients with CP on the basis of the belief that in the experiment, fibers adsorb digestive enzymes, thereby affecting their action [97]. However, this idea is based on indirect data (for example, triolein breath tests, the results of which may be affected by delayed evacuation of gastric contents due to action of fibers) [98].

• Patients with decompensated exocrine pancreatic insufficiency and/or long-standing CP (over 5 years) should be screened for vitamin *deficiencies (A, D, E, and K) and*, if necessary, their parenteral administration is indicated [61].

Grade of Recommendation: C. Evidence level: 5.

Comments: *Patients with CP may experience vitamin malabsorption (A, D, E, and K), accompanied by decreased serum levels [99]. At the same time, clinical manifestations of vitamin deficiency are rare [40, 100]. Patients with CP may develop vitamin B_{12} deficiency, due to a violation of the breakdown of the vitamin B_{12}* complex *with haptocorrin (Castle factor) by the pancreatic proteases. Patients with alcohol abuse also have a risk of developing thiamine (vitamin B_1), riboflavin (vitamin B_2) and pyridoxine (vitamin B_6) deficiency. In the case of low serum vitamins level, vitamin replacement therapy should be prescribed [41–43].*

3.2 Conservative treatment

Conservative treatment of patients with CP is aimed at symptom relief and prevention of complications. At the same time, there are 6 main tasks of conservative therapy of CP [28].

1) cessation of alcohol consumption and stop of smoking, regardless of the suspected disease etiology, duration and daily doses of alcohol and the smoking intensity;

2) determining the cause of abdominal pain and reduction of its intensity;

3) treatment of pancreatic exocrine insufficiency;

4) detection and treatment of endocrine insufficiency in the early stages before the development of complications;

5) nutritional support;

6) screening of pancreatic adenocarcinoma, especially with hereditary (familial) pancreatitis, family history of pancreatic cancer, long history of proven CP, age over 60 years.

Relief of abdominal pain

• Patients with intense pain due to CP are recommended for on-demand or course administration of analgesics (e.g. paracetamol** 1000 mg tid), or non-steroidal anti-inflammatory drugs. At ineffectiveness preference should be given to tramadol** (not more than 400 mg / day). Duration of long-term therapy with paracetamol** — no more than 3 months with monitoring of the patient's physical signs, blood biochemistry [101].

Grade of Recommendation: C. Evidence level: 5.

Comments: *Within 3 months, the pain should stop or decrease when it is possible to take paracetamol** on demand (Algorithm 3). In the event that there is a postprandial increase in pain, analgesics should be taken 30 minutes before meals to minimize the increase in pain after a meal [28, 61]. If the patient does not have a dependence of pain on food intake, analgesics should be taken after meals to reduce the risk of damage to the gastric mucosa.*

• To reduce the manifestations of concomitant depression, reduce the pain severity and potentiate the effect of analgesics, prescription of antidepressants — non-selective tricyclic antidepressants [102].

Grade of Recommendation: C. Evidence level: 5.

Comments: *Antidepressants may alter the sensitivity of central nervous tissue and visceral nerves, which may play a role in the development of pain in CP. Non-selective tricyclic antidepressants due to potential cardiotoxicity and anticholinergic effects*

have a wide profile of adverse events. Since the analgesic effects of antidepressants are class-specific effects, as an alternative, selective serotonin reuptake inhibitors may be considered, but currently there are no RCTs showing their efficacy.

• Pregabalin** used in the treatment of neuropathic pain [103, 104] is recommended for relief of persistent pancreatic pain in CP.

Grade of Recommendation: B. Evidence level: 2.

Comments: *The drug has analgesic and antianxiety effects, which may be an additional positive effect for some patients [103, 104].*

• Patients with CP with dominant abdominal pain, no duct dilation, or minimal changes in the pancreatic parenchyma are advised to prescribe digestive enzyme preparations to reduce pain [105–108].

Grade of Recommendation: C. Evidence level: 2.

Comments: *Trial 6-weeks treatment with high doses of enzymes (uncoated tablets) [23, 28, 109, 110] is unavailable due to the lack of such drugs on pharmaceutical market in Russia. At the same time, controlled studies have obtained little evidence of the effectiveness of such therapy [111] mainly due to the inconsistency of the results [112, 113] partly due to the short period of observation. Randomized trials of recent years indicate reduction of abdominal pain in patients taking pancreatin** capsules at a daily dose of over 240'000 lipase units for 1 [107] and 50 weeks [108, 114].*

*Enteric-coated pancreatin tablets** registered in Russia, has no evidence of efficacy, because it has not been tested in any placebo-controlled study. Most studies have not found the benefits of using enteric-coated macrotables for the relief of pancreatic pain. In comparison, studies using non-enteric-coated tablets showed a reduction in pain compared to placebo. At the same time, a prerequisite for the use of uncoated digestive enzymes is the simultaneous prescription of antisecretory drugs (H_2-histamine receptor blockers or proton pump inhibitors (PPI)), probably capable of decreasing the severity of pancreatic pain [115] and increasing the effectiveness of pancreatin**.*

*A large number of observational, simple comparative and interventional studies have been published suggesting the advisability of prescribing only pancreatin** in* the *form of enteric-coated microparticles in high doses in combination with antisecretory drugs for the relief of pancreatic pain [1, 116, 117], as well as a cross-sectional study showing the benefits of pancreatin capsules** over enteric-coated tablets [118].*

• In the case of the prescription of uncoated digestive enzymes for the pain relief in patients with CP, simultaneous administration of antisecretory drugs (PPIs) is recommended, probably capable of affecting the severity of pancreatic pain [115] and increasing the efficacy of pancreatin**.

Grade of Recommendation: A. Evidence level: 2.

At ineffectiveness of conservative therapy for abdominal pain for 3 months or the need to take opioid analgesics for 2 weeks (due to the high risk of dependence) patient should be examined by surgeon and endoscopist to assess the likelihood of pain relief using endoscopic or surgical treatment techniques [119].

Treatment of exocrine and endocrine pancreatic insufficiency

A clinically significant decrease of absorption of fats and proteins occurs only with decrease in the functional activity of the pancreas by more than 90 % [26]. Surgical resection of the pancreas can also cause the development and/or aggravation of exocrine pancreatic insufficiency [120, 121] and lifelong enzyme replacement therapy. Adequate and timely treatment allows to avoid the development of serious complications and reduce mortality due to malnutrition.

Enzyme replacement therapy. The goal of replacement therapy is to enable the patient to receive, digest and absorb the normal amount of essential nutrients and trace elements. Clinical indications for enzyme replacement therapy for CP:

- verified steatorrhea;
- chronic diarrhea, polyfecaly;
- nutritional deficiency;
- previous pancreatic necrosis, severe CP (calcification of the pancreatic parenchyma or intraductal calcifications in combination to MPD dilation) [122];
- previous pancreatic surgery with alteration of normal food passage (classical pancreatoduodenal resection, Roux-en-Y lateral pancreatic jejunostomy);
- condition after any surgical interventions on the pancreas with exocrine insufficiency signs.

• Enzyme replacement therapy is recommended for patients with CP and exocrine pancreatic insufficiency because they improve fat digestion and absorption [61, 123, 124].

Grade of Recommendation: A. Evidence level: 1.

Comments: *Patients with clinically obvious steatorrhea (abundant semi-liquid, oily sheen, fetid stool) should receive enzyme preparations based on clinical signs [61, 123].*

• All patients with CP and clinical or biochemical signs of nutritional failure, including those without obvious steatorrhea [53, 120] are recommended to prescribe enzyme replacement therapy to normalize nutritional status (vitamin levels vitamin A, D, E, and K levels, prealbumin and ferritin), and to prevent osteoporosis caused by vitamin D malabsorption [40, 100].

Grade of Recommendation: C. Evidence level: 5.

Comments: *To monitor the efficacy of treatment in the world practice, laboratory methods for assessing fat digestion are used: quantitative evaluation of neutral fat content in feces (in clinical studies), breath tests with ^{13}C-mixed triglycerides (in studies and routine practice) [53]. Both methods are not yet available in Russia. At the same time, it is no less effective and more accessible to use BMI and laboratory nutritional markers (serum level of retinol-binding protein, vitamin B_{12}, transferrin, magnesium, zinc, absolute lymphocyte count in the absence of other causes for lymphocytopenia) [84, 85].*

· Enzyme replacement therapy is recommended to improve the quality of life of patients with CP [117, 125–127].

Grade of Recommendation: B. Evidence level: 2.

Comments: *There is a strong relationship between improvement of quality of life, increasing body weight, and reducing the fat excretion with feces* [117, 125–127].

· All patients with CP at enzyme replacement therapy are advised to take pancreatin** during or right after meals [124, 128, 129].

Grade of Recommendation: A. Evidence level: 1.

Comments: *Prescription of average of 40-50 thousand lipase IU for the main meal and 20 thousand IU for snacks leads to normalization of fat absorption, significant increase in body weight, normalization of retinol-binding protein and prealbumin levels in most CP patients [53].*

· Patients with CP for the treatment of malabsorption in exocrine pancreatic insufficiency are advised to take pancreatin capsules** containing microparticles (microtablets, minimicrospheres, etc.) with enteric coating [107, 108, 114].

Grade of Recommendation: B. Evidence level: 1.

Comments: *Pancreatin capsules with enteric-coated microparticles* are *significantly more effective than tablets in the treatment of steatorrhea because improved pharmacokinetics are available to provide more likely contact of enzymes with chyme and larger surface area [130].*

· In patients with exocrine pancreatic insufficiency signs, recommended minimal dose for initial treatment is 25–40 thousand IU lipase units for the main meal and 10–25 thousand IU lipase — for an intermediate meal, overall — at least 5 times per day [114, 124, 129].

Grade of Recommendation: A. Evidence level: 1.

Comments: *Prognosis for enzyme replacement therapy effectiveness is definitely affected by the choice of the drug. The patient should receive at least 25–40 thousand lipase IU at the main meal and 10–25 thousand IU lipase per snack [28, 61].*

· All patients with CP receiving enzyme replacement therapy should be monitored to evaluate the initial treatment efficacy by weight gain and reduction in symptom severity 6 months after the start of therapy; however, any doubts about the efficacy of replacement therapy should be regarded as indications for laboratory and instrumental control of enzyme replacement therapy [74].

Grade of Recommendation: C. Evidence level: 5.

Comments: *Clinical markers: relief of diarrhea, normalization of dyspeptic symptoms are often used as criteria for assessing the efficacy of enzyme replacement therapy, [61]. At the same time, in many patients, the normalization of stool occurs at the doses of enzymes that are insufficient to normalize fat digestion.*

· If patients receiving the maximum doses of enteric-coated of digestive enzymes do not achieve symptomatic response, it is recommended to prescribe antisecretory drugs — PPIs in standard doses [115, 120, 124, 131].

Grade of Recommendation: A. Evidence level: 1.

Comments: *Patients with persistent symptoms, despite initial doses of modern enteric-coated digestive enzymes (25–40 thousand lipase units for the main meals and 10-25 thousand lipase units for snacks), should double the doses of pancreatin capsules** or prescribe antisecretory drugs [130] to improve fat emulsification [115, 120, 131]. Preferred drugs are PPIs in standard doses (e.g.: #omeprazole** 20 mg × bid). There are some small studies demonstrating the effectiveness of such approach in patients with severe pancreatic insufficiency [131–133].*

· With persistent steatorrhea in patients with CP, it is recommended to exclude other causes of diarrhea, in particular those associated with small intestinal bacterial overgrowth, frequent in CP [134] invasion of protozoa, celiac disease.

Grade of Recommendation: C. Evidence level: 4.

· In patients with severe pancreatic insufficiency after pancreatic necrosis, either in the presence of calcifying pancreatitis, or in patients with significantly reduced fecal elastase-1 (less than 200 ug/g), lifelong replacement therapy in selected dose *[61, 122].*

Grade of Recommendation: C. Evidence level: 5.

Comments: *In proven CP with signs of nutritional deficiency (weight loss, muscle hypotrophy, osteoporosis, signs of vitamin deficiency), prescription of enzyme replacement therapy may be*

indicated even without steatorrhea verification [61, 122].

• When treating patients with CP-related diabetes, it is recommended to monitor blood glucose levels to prevent complications, avoiding the development of hypoglycemia and ketoacidosis *[28, 55].*

Grade of Recommendation: C. Evidence level: 5.

Comments: *In the development of diabetes in the outcome of severe fibrosis of the pancreatic parenchyma, oral hypoglycemic agents do not play a significant role [28, 55]. Most patients with pancreatic diabetes and the inefficacy of the corresponding diet require the insulin prescription [29]. The diet for pancreatic diabetes mellitus corresponds to that for type 1 diabetes, with the exception of the requirement to correct malabsorption, vitamin deficiency and trace elements; fractional nutrition may prevent hypoglycemia [61].*

3.3. Surgical treatment

Surgical treatment: indications and methods

With complicated course of the disease, as well as in some cases with non-stop abdominal pain, endoscopic or surgical treatment [61]. The decision to perform the intervention should be made in a center specializing in conservative and surgical methods of treating pancreatic diseases.

Complications of CP include: 1) persistent pain syndrome, not amenable to drug therapy; 2) ductal hypertension of the pancreas for MPD stones or strictures of the pancreatic duct; 3) symptomatic postnecrotic cysts of the pancreas; 4) mechanical jaundice caused by TCBD compression; 4) portal hypertension due to compression of the portal vein confluence or thrombosis of the splenic vein; 5) persistent violation of the passage of food through the duodenum; 6) pseudoaneurysm of the celiac trunk branches and the superior mesenteric artery [135-140]. At the background of these complications, pancreatic ascites and/or pleurisy may occur; in patients operated for pancreatitis or who have suffered a pancreas injury — pancreatic fistulas requiring surgical treatment [141–144]. An unconditional indication for surgical treatment is the inability to exclude pancreatic cancer.

In the treatment of symptomatic pseudocysts, surgical and endoscopic methods are effective [33]. In the surgical treatment of pseudocysts, jejunum or stomach Roux-en-Y anastomosis can be applied, and a lateral pancreatojejunostomy is performed with concomitant dilatation of MPD (>7 mm) [145].

Recurrent jaundice or clinical picture of cholangitis is an indication for endoscopic stent-endoprosthesis, which is a safe and effective procedure (with complication rate of 4 to 7 %) [146] installation of stent-endoprosthesis, full resolution of the bile duct stricture can be achieved only in a small proportion of patients, especially with calcifying pancreatitis. The best results are achieved with the phased placement of several stent-endoprostheses [65].

In the case of isolated duodenal obstruction (up to 1 % CP patients) gastrojejunostomy is carried out [147]. At combination of duodenal obstruction with other complications of CP (pain and/or bile duct obstruction), duodenum/pyloric-preserving resection is performed.

RCTs compared to the effectiveness of surgical and endoscopic drainage of the biliary tract in CP were not performed.

Thus, in the absence of data for pancreatic cancer, surgery should be the treatment of choice in the presence of biliary tract stricture with clinical manifestations of jaundice lasting more than one month. The optimal procedure has not yet been determined. Various operations are performed from the creation of a bypass biliary anastomosis (choledocho- or hepatojejunostomy) to PDR. In the presence of inflammatory formation and/or suspected cancer, in all cases, resection of the pancreatic head should be performed [61].

With *uncomplicated* disease *course*, invasive interventions are aimed at correcting morphological changes in the pancreatic duct system (strictures, stones), inflammatory changes in the parenchyma or performing neurolysis.

Pain management. Prospective RCTs compared efficacy of conservative and surgical treatment of pain in CP have not been conducted. Studies evaluating the dynamics of pain after surgical treatment have noted greater variability in effect (from 47 to 80 % of patients) [24, 88].

• In patients with verified CP, it is recommended to consider of performing surgical intervention in the following conditions: intense unpurchased abdominal pain, leading to a decrease or loss of ability to work; lack of effect from conservative treatment for 3 months; the risk of developing dependence on analgesics and/or psychotropic drugs; the occurrence of complications of CP that require invasive elimination (bleeding, duodenal obstruction, symptomatic pseudocysts, etc.); suspected pancreatic cancer [91, 148–155].

Evidence level: 1. Grade of Recommendation: A.

Comments: *In seven randomized trials, meta-analyses [91, 148, 151–155] a total of 302 patients had a significant pain reduction [149, 150]. In patients with asymptomatic CP and duct dilatation (>7 mm), surgical decompression of the pancreatic duct is not mandatory, but it can be carried out to prevent progression of exocrine and endocrine insufficiency [61]. If it is impossible to exclude cancer, resection is indicated to obtain material for histological examination. Untimely diagnosis of*

pancreatic cancer significantly worsens the prognosis [156].

• Surgical treatment of patients with CP is recommended with the ineffectiveness of the consistent use of conservative methods for 3 months (strict adherence to the diet, therapy with encapsulated pancreatin**, vitamins, analgesics, incl. tramadol**, antidepressants, pregabalin**), with significant decrease in the quality of life and disability [28].

Evidence level: 5, Grade of recommendations is C.

Comments: *The decision to intervene should be carefully weighed against the assessment of the risk of early and long-term complications. Other causes of pain in the upper gastrointestinal tract should be excluded.*

Endoscopic treatment

• Patients with asymptomatic dilation of the pancreatic duct are not candidates for endoscopic treatment [74].

Grade of Recommendation: C. Evidence level: 5.

Comments: *There are no studies to assess the effects of endoscopic treatment on endocrine and exocrine pancreatic function in these patients [61].*

• Endoscopic treatment is recommended in patients with pain and dilatation of the pancreatic duct in order to eliminate pain *[157, 158].*

Grade of Recommendation: C. Evidence level: 4.

Comments: *Prospective studies indicate the effectiveness of endoscopic treatment in patients with pain and dilatation of the pancreatic duct [157, 158].*

Endoscopic stenting of the main pancreatic duct (ESMPD)

• Lithoextraction and mechanical lithotripsy are recommended for solitary MPD stones under 5 mm in size, located at the level of pancreatic head *[56, 157, 158].*

Evidence level: 4, Grade of recommendations is C.

Comments: *For the purpose of fragmentation of MPD stones, shock wave lithotripsy is used (in the presence of X-ray contrast stones in the main pancreatic duct), shock wave lithotripsy is possible with subsequent ERCP, virsungotomy and lithoextraction or contact lithotripsy (mechanical, laser or electrohydraulic [56, 76, 159–163].*

• ESMPD with the help of pancreatic polymer stents is recommended for patients in the presence of dominant stricture and prestenotic dilation of the duct of at least 6 mm. It is recommended to install one or more stents of 7 Fr, 8.5 Fr or 10 Fr with replacement with 2 to 5 months interval, depending on the diameter and number of stents while maintaining the final total diameter for a period of at least 1 year. Before performing stenting, endoscopic virsungotomy, mechanical and/or balloon dilatation of the stricture is recommended. The presence of multiple strictures is a contraindication to duct stenting [56, 76, 159, 164].

Grade of Recommendation: C. Evidence level: 5.

Comments: *Stenting of the pancreatic duct is advisable to perform in the presence of significant strictures — an increase in the diameter of the duct more distal than the stricture. The presence of multiple strictures and multiple MPD stones is a contraindication to stenting of the pancreatic duct. For successful stenting, it is required to perform pancreatic sphincterotomy and dilatation of the stricture, eliminate MPD stones and strictures of the pancreatic duct. Stenting is carried out by polymer pancreatic stents with diameter of 7–10 Fr, the length and shape of which are selected individually. Obturation of polymeric pancreatic stents occurs after 2–5 months, depending on their diameter and number, which requires their replacement [159, 165, 166]. Complications of pancreatic duct stenting (exacerbation of pancreatitis, proximal or distal stent migration, pancreatic abscess) are observed in 6 to 39 % of cases [56, 76].*

In case of recurrence of pain, repeated endoscopic procedures are highly effective [167]. Endoscopic drainage may be proposed as a method of choice in patients with minor changes in the pancreas parenchyma and the absence of multiple complications of CP, as well as in patients with contraindications to surgery or refusal to do so, as well as be a preliminary stage for assessing the effectiveness of the planned surgical treatment [152].

In patients with frequent bouts of pain, a sphincterotomy can be performed to improve the outflow of pancreatic secretion. However, there is no data on the effectiveness of this method for treating pain in patients without duct dilatation and obstruction.

Currently, there are two strategies for main pancreatic duct stenting:

- removal of the stent after 6–12 months, regardless of the resolution of the pancreatic duct stricture;
- subsequent stent replacements until the stricture disappears.

Relief of pain within 12 months after stenting is achieved in 2/3 of patients, but the complete disappearance of strictures was observed in a small proportion of patients [167]. A promising approach is an accurate measurement of the stricture of the distal part of the pancreatic duct with a stepwise installation of stents of increasing diameter (an increase in size by 2–4 units every 6 months). After the final removal of the stent established by this technique, the disappearance of the stricture was

observed in 95 % of cases [168]. At the same time, such aggressive endoscopic treatment with the sequential installation of several polymeric pancreatic stents can lead to the resolution of stricture in 44–90 % of cases, followed by a relapse-free course within 13–48 months. after removal of the pancreatic stent [78, 185].

· In the absence of the effect of endoscopic stenting of the pancreatic duct or a relapse of intense abdominal pain, surgical treatment is recommended for patients [61, 65, 169, 170].

Evidence level: 4. Grade of Recommendation: C.

· Endoscopic treatment is recommended as a temporary measure to effectively treat cholestasis, jaundice, or cholangitis in patients with CP [61, 65, 169, 170].

Evidence level: 5, Grade of recommendation: C.

Comments: *The shortness of the stent's presence in the common bile duct is determined by frequent complications — occlusion, stent migration, suppurative and septic conditions [61]. Complete elimination of biliary stricture in the long term of observation according to prospective studies was noted in no more than 10 % of patients [184].*

· Endoscopic treatment is recommended for pancreatic pseudocysts with the presence of clinical manifestations, as well as for complicated non-hemorrhagic pseudocysts [32, 61].

Evidence level: 4, Grade of recommendation: C.

Comments: *Treatment of asymptomatic and uncomplicated pseudocysts is not indicated, regardless of their size [32]. Endoscopic drainage may be preferable to surgical treatment because it has a better benefit/risk profile, being a less invasive method that provides drainage of similar efficacy [61].*

Endoscopic treatment of external and internal pancreatic fistulas

· Endoscopic drainage of the pancreatic duct in pancreatic fistulas is recommended for patients in the presence of a duct defect confirmed by fistulography and MRCP data in order to overlap the area of damage to the duct with a stent [165, 171].

Grade of Recommendation: C. Evidence level: 4.

Comments: *External pancreatic fistulas occur, as a rule, after external drainage of postnecrotic pancreatic cysts, less often — after pancreatic surgery. One of the rare complications of CP are internal fistulas of the pancreas, which open into the abdominal and sometimes thoracic cavities. One should strive for stenting (drainage) with overlapping of the area of damage to the duct. Installation of a stent or silicone drainage for nasopancreatic drainage is proximal to the defect, as well as isolated virsungotomy is also possible, but is less effective. The recommended period of stenting in cases of absence of a stenosing intraductal component (strictures) is at least 6 weeks* [172].

Draining operations for pancreatic postnecrotic/parapancreatic pancreatic cyst

Indications for drainage of a postnecrotic cyst are its size of more than 5 cm, abscessing, pain, impaired outflow of bile or stomach obstruction, portal hypertension, perforation of a postnecrotic cyst into the abdominal cavity. Postnecrotic asymptomatic cysts with a diameter of less than 5 cm with an unformed capsule and not communicating with the duct of the pancreas tend to self-heal, so patients are subject to dynamic observation [171, 173, 174]. The elimination of cysts can be performed through internal endoscopic drainage into the lumen of the duodenum or stomach, as well as "open" surgical access.

· External drainage of a postnecrotic cyst is recommended in abscessing, the absence of a formed capsule or the ability to perform a more complex intervention due to the severity of the patient's condition or technical reasons [171, 173, 174].

Grade of Recommendation: C. Evidence level: 5.

Comments: *External drainage under ultrasound guidance is a coerced measure and is indicated only for abscessing, opening a cyst into the abdominal cavity or an extremely serious condition of the patient. The outcome of external drainage of a postnecrotic cyst, as a rule, is the formation of an external pancreatic fistula, which subsequently often requires surgical treatment [57]. The tactics of surgical treatment are determined by the severity of the cyst wall, the presence or absence of sequesters and infection in the lumen of the cyst, the technical equipment and level of qualification of surgical personnel.*

· Endoscopic internal drainage of a postnecrotic pancreatic cyst is recommended when the cyst size is more than 5 cm without a tendency to regress within 6 weeks after its occurrence, the cyst wall is more than 5 mm, the absence of large sequesters in its lumen, close application of the cyst cavity to the wall of the stomach or duodenum [173, 174].

Grade of Recommendation: C. Evidence level: 4.

Comments: *Transmural access is recommended under endosonographic control, which allows you to choose a safe route for puncture. For drainage, self-expanding nitinol fully covered stents (biliary nitinol coated stents) should be used that have elements for internal fixation, which prevents stent migration. It is possible to use at least 2 biliary plastic stents with bilateral fixatives of the "double pigtail" type (plastic stents-endoprostheses to maintain the patency of the bile ducts in sets and individual packages). Stents should not be removed until instrumental confirmation of the collapse of*

the cyst walls and earlier than 1-2 months after their implantation. This method allows you to succeed in 92 % of cases. However, the immediate results are better than long-term ones, relapses occur in 8.5–23.0 %, complications – 14.4 % [159, 171].

Transpapillary access with cystoduodenal stenting is used for small (up to 5 cm) collections associated with the pancreatic duct at the level of the head [159, 171].

· Cystopancreatoeyunostomy in an "open" way or through mini-access is recommended for postnecrotic cysts of large size of any localization with the presence of a well-formed capsule, large sequestrations [175, 176].

Grade of Recommendation: A. Evidence level: 1.

Comments: *Cystopancreatojejunostomy provides recovery in 90–100 % of cases in the absence of fibrotic changes in pancreatic tissue proximal to postnecrotic cysts. Postoperative complications occur in 20 % of observations [174, 175]. Preference should be given to minimally invasive accesses. Cyst anastomosis should be performed with a Roux-en-Y loop of the jejunum with a length of at least 70 cm in a single-row wrapped suture thread of synthetic monofilament resorptive. Roux-en-Y loop of the jejunum is placed behind the colon, when shortening or involving in the inflammatory infiltrate of the mesentery of the transverse colon, – in front of the intestine. Interintestinal anastomosis end-to-side is imposed at the level of the first or second vascular arcade of the mesentery of the jejunum. The walls of the cyst are partially excised, and necessarily undergoes a pathological study to exclude the presence of a cystic tumor of the pancreas. Laparoscopic cystopancreatojejunostomy can be performed only in centers with the necessary experience in laparoscopic operations.*

Treatment of biliary hypertension in chronic pancreatitis

· Endoscopic elimination of biliary hypertension in chronic pancreatitis is recommended for clinically significant cholangitis and mechanical jaundice. Bile duct placement is a temporary measure and is performed with multiple biliary plastic stents. Every 3 months, stent replacement is required. The course of treatment is at least 1 year after reaching the location of the maximum number of stents in the lumen of the biliary tree [159, 171, 177].

Grade of Recommendation: A. Evidence level: 2.

Comments: *With the ineffectiveness of previous endoscopic stenting and non-compliance with the patient's treatment regimen, endoscopic treatment is not indicated. Patients require dynamic observation because of the risk of developing septic complications associated with occlusion or migration of stents. It is unacceptable to use uncovered and partially covered biliary nitinol stent-endoprostheses as a final method of treatment due to the short duration of the stent functioning and the impossibility of its endoscopic extraction. With a high short-term clinical effect (up to 92 %), the effectiveness of endoscopic stenting in the long term, compared with the surgical method, is low (31–62 %), and therefore biliary stenting is recommended for the purpose of preoperative preparation or in case of refusal of surgery* [159, 171, 177].

Surgical treatment of pancreatic hypertension, MPD stones

· Lateral pancreaticojejunostomy is recommended in the presence of ductal hypertension and expansion of the pancreatic duct due to its strictures or stones at the level of the isthmus, body and tail of the pancreas and the absence of fibrous degeneration of the head and uncinate process of the pancreas. In the presence of a cyst and pancreatic hypertension, a combination of interventions is possible – Roux-en-Y lateral cystopancreatojejunostomy [56, 76, 138, 139, 175].

Grade of recommendations: A. Level of reliability of evidence: 1.

Comments: *Lateral pancreaticojejunostomy allows you to reliably eliminate ductal hypertension at the level of the dorsal segment of the head, body and tail of the pancreas. With fibrous degeneration of the parenchyma of the head and uncinate process of the pancreas, the presence of stones or strictures in the terminal part of the duct of the pancreas, this operation is not effective. Since in most cases with CP the greatest sclerotic changes occur precisely in the pancreatic head, indications for longitudinal pancreatojejunostomy are rare. Lumen of the pancreatic duct is opened all the way – from the head to the tail of the pancreas. Hemostasis with capillary bleeding is provided by coagulation, bleeding arterial and venous vessels are stitched. Stones are removed from the duct of the pancreas and its branches. In case of difficulties in detecting the duct of the gland, as well as to assess the radicality of the operation, intraoperative ultrasound should be performed. The pancreatic parenchyma, even in the presence of intraparenchymal calcifications, is not excised. Pancreatojejunoanastomosis with isolated Roux-en-Y loop of the intestine is formed by a continuous suture of a synthetic monofilament absorbable thread. The Roux-en-Y loop is carried out through a window in the mesentery of the transverse colon.*

Resection operations for chronic pancreatitis

Resection interventions on the pancreas are currently well developed and are a priority, since they can radically eliminate the complications of CP caused by fibrocystic degeneration of the pancreatic

head or distal departments [56, 76, 138, 139, 175]. There are several options for resection of the pancreatic head, each of which has strict indications [56, 76, 138, 139, 175, 178–180].

• Resection of the pancreatic head with longitudinal pancreatojejunoanastomosis (Frey's operation) is recommended for fibrous transformation of the pancreas head, pancreatic hypertension caused by virsungolithiasis or ductal strictures [56, 76, 138, 139, 175, 178].

Grade of Recommendation: A. Evidence level: 1.

Comments: *Resection of the pancreatic head with longitudinal pancreatic jejunoanastomosis (Frey's operation) provides a reliable elimination of pancreatic hypertension and removal of most of the sclerosed tissue of the pancreatic head, as proposed in the version of the operation modified in 2003 [180]. The duct of the pancreas is opened throughout. The tissue of the head and uncinate process is excised, while maintaining no more than 5 mm of parenchyma adjacent to the wall of the duodenum, the intramural part of the common bile duct and portal vein, remove the stones from the duct of the pancreas and lateral ducts, as far as possible. With the edges of the resulting cavity in the pancreatic head and the opened duct of the pancreas, an anastomosis is formed with the Roux-en-Y of the jejunum with a continuous wrapping suture absorbable synthetic monofilament suture material. A Roux-en-Y at least 60 cm long is conducted through the mesentery of the transverse colon. This operation does not provide a complete exposure from the tissue of the pancreas of the terminal section of the common bile duct and portal vein. Due to the large wound surface in the resection zone of the head, uncinate process and dissected duct of the pancreas in the immediate postoperative period, there is a danger of early bleeding into the lumen of the anastomosis [179, 180].*

• The Berne modification of the resection of the pancreatic head is recommended in the presence of not only fibrous degeneration of the parenchyma of the head, but also biliary hypertension [139, 178–181].

Grade of Recommendation: C. Evidence level: 5.

Comments: *With the Berne modification of the resection of the pancreatic head, the volume of the removed pancreatic tissue increases due to the complete excision of the parenchyma adjacent to the intramural part of the common bile duct [181]. In the presence of bile hypertension, mechanical jaundice, the lumen of the bile duct can be opened. The resulting flaps of the bile duct wall are sewn to the remaining gland tissue. The duct of the pancreas, if there are stones or strictures in it, dissected, as in Frey's operation. The Roux-en-Y of the jejunum is sewn along the perimeter of the resected head, uncinate process and MPD. The disadvantage of this operation is the risk of a stricture of the common bile duct inside the cavity of the anastomosis [76, 140]. In the presence of an extended stricture of the common bile duct, it is impractical to open its lumen in the cavity formed after resection of the head. The most reliable way to eliminate biliary hypertension is the formation of hepaticojejunoanastomosis on* Roux-en-Y *loop of the jejunum.*

• Subtotal Beger resection of the pancreatic head is recommended in the presence of these complications in combination with portal hypertension due to compression of the confluence of the superior mesenteric and splenic veins [76, 140, 179–181].

Grade of Recommendation: A. Evidence level: 1.

Comments: *The pancreas is mobilized in the region of the isthmus, under which a tunnel is created, exposing the anterior surface of the confluence of the portal vein. The portal and upper mesenteric vein are isolated from the cicatricial case surrounding and squeezing the veins. The tissue of the head and uncinate process is resected with the leave of a strip of parenchyma along the medial wall of the duodenum and the terminal part of the common bile duct no more than 5 mm thick. The stump of the gland body and the remains of the parenchyma along the wall jejunal loop anastomositis with the Roux-en-Y of the jejunum with two joints, and with a small volume of proximal stump of the pancreas, there is no need for its anastomosis with the intestine [179–181].*

• Pancreatoduodenal resection is recommended in cases where it is not possible to exclude the presence of a malignant tumor of the pancreatic head, as well as with fibrocystic changes in the pancreatic head in combination with persistent duodenal stenosis that is not amenable to conservative therapy [139, 175, 179–184].

Evidence level: 1, Grade of Recommendation: A.

• Distal resection of the pancreas is recommended in cases where it is not possible to exclude the presence of a tumor of the tail of the pancreas, with postnecrotic pancreatic cyst, replacing the parenchyma of the distal part of the organ [139, 175].

Grade of Recommendation: A. Evidence level: 1.

Comments: *Distal resection of the pancreas in CP is performed in cases where it is not possible to exclude the presence of a tumor of the tail of the pancreas; in rare cases — with postnecrotic cysts that completely replace the tail of the pancreas, provided that there is no violation of the outflow of secretion through the duct of the pancreas in the body and pancreatic head. When performing distal resection of the pancreas, in cases where the splenic vessels can be separated from the walls of the postnecrotic cyst, splenectomy should be avoided.*

In the presence of subhepatic portal hypertension caused by thrombosis of the splenic vein with varicose veins of the stomach fundus, splenectomy with one of the types of resection-draining intervention is indicated [139, 175].

· When performing resection intervention for CP, it is recommended to perform a pathological examination of the resected pancreatic specimen [47, 90].

Grade of Recommendation: C. Evidence level: 5.

Endovascular interventions for pseudoaneurysms of the celiac trunk basin and the superior mesenteric artery

· Patients with PA branches of the celiac trunk and superior mesenteric artery that have a connection with the pancreatic duct (PA type 1) are recommended a two-stage treatment: endovascular "disconnection" of the aneurysm cavity from the bloodstream, followed by radical surgical treatment of complications of CP. In the presence of type 2 PA, which is not connected to MPD, it is possible to perform endovascular surgery aimed at closing the aneurysm cavity or endoprosthesis of the artery with a coated nitinol stent, which will be the final stage of treatment [185–187].

Grade of Recommendation: C. Evidence level: 4.

Comments: *Patients with PA type 1 at the time of diagnosis are often in serious condition due to anemia due to recurrent intestinal bleeding. Due to the severity of the patients' condition, radical surgical treatment cannot be performed. At the first stage of treatment, it is necessary to stop recurrent bleeding through urgent endovascular intervention [185–187]. The following options for endovascular interventions are recommended: occlusion of the artery distal and proximal to the neck of the aneurysm; occlusion of the aneurysm cavity and afferent artery; endoprosthetics of the artery with a coated stent at the level of the neck of the aneurysm. Endovascular "shutdown" of PA from the bloodstream allows you to eliminate recurrent intestinal bleeding. However, due to the communication of the PA type 1 cavity with the lumen of the pancreatic duct, the effect of pancreatic juice leads to the lysis of thrombotic masses 2–3 weeks after embolization (except in cases where endoprosthetics with a coated stent is performed) [186]. After intensive preparation aimed at eliminating anemia and hypoproteinemia, it is necessary to carry out radical surgical intervention aimed at eliminating complications of CP, which led to the emergence of PA.*

Postoperative complications

Operations for CP are accompanied by a large number of postoperative complications, reaching 20–40 % [188]. In cases where the pancreatic parenchyma at the time of surgery has not lost exocrine activity, there is a real threat of postoperative pancreatitis and the formation of a pancreatic fistula [175]. Extensive resections of the pancreatic head with a large area of the wound surface create conditions for the occurrence of early bleeding into the lumen of pancreatic jejunoanastomosis.

Postoperative pancreatitis

Postoperative pancreatitis is a frequent complication after pancreatic surgery. Macroscopic manifestations of pancreatitis in the form of vitreous edema of parapancreatic tissue and even plaques of steatonecrosis can be recorded already during surgery [188] In the immediate postoperative period, clinical signs of pancreatitis are manifestations of endogenous intoxication (persistent tachycardia in the absence of hypovolemia, acrocyanosis, inhibition of spontaneous breathing), discharge from the abdominal cavity through drainage tubes of brown exudate with high content of amylase, gastrostasis and paralytic intestinal obstruction. The listed symptoms indicate the development of severe pancreatitis. The biochemical marker of pancreatitis is an increase in the level of amylase in the blood over 500 u/l. Treatment of postoperative pancreatitis should be conservative and carried out in the intensive care unit [189, 190].

· In postoperative pancreatitis, patients who have undergone surgery for the pancreas are recommended to conduct intensive conservative therapy in the intensive care unit in order to eliminate signs of hyperamylasemia and endogenous intoxication [190].

Grade of Recommendation: C. Evidence level: 4.

Comments: *The scheme of basic conservative therapy includes antibiotic therapy for the prevention and treatment of septic complications; drug suppression of the secretion of the pancreas, stomach and duodenum; elimination of hypovolemia with correction of water-electrolyte and metabolic disorders; improvement of rheological properties of the blood; prevention and treatment of functional insufficiency of the gastrointestinal tract; analgesic and anti-enzymatic therapy. With pancreatic necrosis it is advisable to use extracorporeal methods of detoxification [188–190].*

· For the prevention of complications, patients who have undergone surgery for the pancreas are recommended the prescription of octreotide** in accordance with the instructions for a particular drug [90, 203, 227].

Grade of Recommendation: B. Evidence level: 2.

Comments: *The use of octreotide** in patients with postoperative pancreatitis significantly reduces the level of pro-inflammatory mediators and cytokines in the blood serum (TNF-α, IL-1, IL-6, IL-8), and also reduces the level of systemic inflammatory response [203].*

Pancreatic fistula

• With pancreatic fistulas, conservative therapy and dynamic observation are recommended to ensure adequate outflow of pancreatic secretions. In the presence of pancreatic fistula, there is a real threat of arrosion bleeding [141–143].

Grade of Recommendation: C. Evidence level: 4.

Comments: *Pancreatic fistula is the result of postoperative pancreatitis, against which there is a failure of the sutures of pancreatodigestive anastomosis or pancreatic stump after distal resections [143]. According to the revision* of the *ISGPF* classification *of 2017, pancreatic fistulas are divided into 3 types: clinically insignificant pancreatic fistula (former type A according to the ISGPF* classification *of 2005). B and C [191, 192].*

Intra-abdominal and intestinal bleeding

• With follow operative non-intense bleeding, conservative therapy is recommended aimed at correcting hemodynamics and the hemostasis system. To clarify the source of bleeding, CT with contrast and/or angiography should be performed [193–198].

Evidence level: 4, Grade of recommendations: C.

• If a bleeding artery is detected during an angiographic examination, endovascular hemostasis [193–198].

Evidence level: 2, Grade of recommendations: B.

• With intense bleeding and the inability to perform endovascular intervention, it is recommended to perform relaparotomy in order to identify the source of bleeding. With bleeding from soft tissues and in the absence of pancreatic necrosis, necrotic parapancreatitis, it is possible to ensure hemostasis by stitching. With arrosion bleeding from the main vessels (mesenteric portal trunk, splenic vein, arteries of the celiac trunk basin and upper mesenteric arteries), resulting from postoperative pancreatic necrosis, it is possible to perform pancreatectomy and splenectomy [193–198].

Evidence level: 2, Grade of recommendations: B.

Comments: *The probability of bleeding after resection operations on the pancreas reaches 10 %, while the mortality rate is 1.2 % [196, 197]. (Level of reliability of evidence 2, Grade of recommendations B). Adequate external drainage of the surgical zone reduces the risk of developing arrosive bleeding.*

Bleeding after pancreatic resection surgery should be classified according to the recommendations of the international group of researchers in the field of pancreatic surgery (ISGPS) [192, 193] taking into account the following factors:

1 — the time of onset of bleeding — the first 24 hours after the completion of the operation — early bleeding; later than 24 hours is arrosive as a rule;

2 — the severity of bleeding — the patient's condition, the level of hemoglobin and the need for transfusion of blood components;

3 — the source and localization of bleeding — intraluminal (into the lumen of the gastrointestinal tract), or intra-abdominal bleeding [191–193].

Bleeding onset time (ISGPS, 2007):

- early — occurs in the first 24 hours after surgery, caused by technical reasons: inadequate hemostasis during surgery, coagulopathy, damage to the vessel wall by coagulation when performing lymphatic dissection;

- later — occurs more than 24 hours after the end of the operation; the causes of bleeding are postoperative pancreatitis and pancreatic fistula, intra-abdominal abscesses, ulcerations at the site of anastomosis, the formation of arterial pseudoaneurysms [192].

In a multicenter study conducted by E. Yekebas (2007) based on the analysis of 1669 resection interventions for the pancreas, the classification of bleeding according to the severity of ISGPS [198].

1. "Sentinel bleeding", characterized by a short flow of a small amount of blood through the drains from the abdominal cavity or nasogastric tube, there may be vomiting of "coffee grounds" or melena; there are no clinical manifestations of acute blood loss (tachycardia, lowering blood pressure), the hemoglobin level does not decrease by more than 15 g/l. Bleeding stops on its own, there is no need for blood transfusion. In this case, recurrence of bleeding is possible within 12 hours.

2. Non-intensive post-resection bleeding is characterized by blood flow through drains from the abdominal cavity, a decrease in hemoglobin levels to 30 g/l, the presence of clinical manifestations of acute blood loss or without them.

3. Intensive post-resection bleeding is characterized by a decrease in hemoglobin levels of more than 30 g/l, the presence of pronounced clinical manifestations of acute blood loss [192].

Early postoperative bleeding. A specific feature of operations in CP (longitudinal pancreatojejunostomy, Frey's operation, the Berne modification of the resection of the pancreatic head) is the formation of a large wound surface of the pancreatic parenchyma and a significant length of dissection of the wall of the jejunum used for anastomosis. As a result, in the immediate postoperative period, bleeding may occur into the lumen of the anastomosis both from the pancreatic parenchyma and the wall of the jejunum. Clinical manifestations are reduced to severe pain in the upper abdomen. As a result, in the early postoperative period, bleeding may occur in the lumen of the anastomosis both

from the pancreatic parenchyma and the wall of the jejunum. Clinical manifestations are reduced to severe pain in the upper abdomen due to blood overstretching of the Roux-en-Y, general symptoms of acute blood loss and melena.

Early non-intense bleeding into the lumen of pancreatic jejunoanastomosis is subject to conservative treatment. With intense bleeding, an emergency angiographic examination should be performed, followed by embolization of the bleeding vessel. If it is not possible to perform endovascular intervention, relaparotomy is performed. With relaparotomy, it is necessary to separate the anterior lip of pancreatojejunoanastomosis and stitch the bleeding vessel, and then perform reanastomosing. It is unacceptable to do enterotomy through the anterior lip of the anastomosis, as this inevitably leads to the failure of the sutures due to a violation of the blood supply to the intestinal wall.

Late postoperative bleeding. Later bleeding, which is arrosic, creates a real threat to the life of the patient and requires conservative therapy for non-intensive bleeding, and with intensive — emergency endovascular intervention with embolization of an arrosed vessel or emergency relaparotomy [199]. With relaparotomy, it is necessary to take into account the state of pancreatic degenerative anastomosis, pancreatic stump and parapancreatic tissue. Bleeding at the time of surgery can be taken into account to cease, which makes it very difficult to identify its source. Postoperative pancreatic necrosis and necrotic parapancreatitis, in combination with arrosion bleeding from the great vessels, is an unfavorable factor and, as an exclusive measure, may require the performance of pancreatic extirpation and splenectomy.

4. Medical rehabilitation, medical indications and contraindications to the use of rehabilitation methods

· For patients with preserved exocrine pancreatic function after the termination of the relapse of CP prescription of digestive enzyme preparations in a daily dose of 100–150 thousand lipase units per day for 3–6 months is recommended [92].

Grade of Recommendation: B. Evidence level: 2.

· With the development of exocrine pancreatic insufficiency, patients with CP are recommended lifelong enzyme replacement therapy, often with the addition of PPN (for example: #omeprazole** from 10 to 40 mg bid) to increase the efficacy of digestive enzyme [111, 112, 116–118].

Grade of Recommendation: C. Evidence level: 4.

Comments: *The further prognosis for patients with CP is determined by the possible development of complications requiring surgical correction (associated to corresponding intraoperative mortality rate). The standardized mortality rate of patients with CP is 3.6: 1 (i.e., patients with any form of CP die 3.6 times more often than people of the same age from the general population) [200].*

· All patients preparing for surgery for CP are recommended to carry out the prevention of infectious complications with broad-spectrum antibacterial drugs 30 minutes before surgery (in the absence of medical contraindications) [195, 201, 202].

Grade of Recommendation: C. Evidence level: 4.

Comments: *Postoperative rehabilitation of patients with chronic pancreatitis complies with the principles of accelerated rehabilitation after surgery (ERAS- early recovery after surgery). Recent studies have shown that the ERAS* program *reduces the length of hospital stay by 30–50 %. At the same time, there is also a decrease in the postoperative complications rate by 40 % [195, 202–204].*

· Early postoperative activation is recommended to all patients operated for complicated chronic pancreatitis to reduce the risk of postoperative complications [202–205].

Grade of Recommendation: B. Evidence level: 2.

Comments: *Bed rest increases the risk of deep vein thrombosis, atelectasis and hypostatic pneumonia, contributes to impaired microcirculation and increases the risk of cardiovascular complications in the postoperative period [33]. The patient can be activated and transferred to upright position during the first 4 hours after surgery [26, 28]. Of particular importance is early physical activation for patients with a high risk of developing postoperative complications. Early activation involves the transfer of patients from the intensive care unit to the specialized department the day after surgery at "smooth" early postoperative period, independent physical activity within the ward.*

· All patients operated for complicated forms of chronic pancreatitis should undergo multimodal analgesia for painless activation and accelerated rehabilitation [202–205].

Grade of Recommendation: B. Evidence level: 2.

Comments: *The multimodal analgesia strategy provides a parallel effect for all parts of the pathogenesis of pain and includes the paracetamol** prescription along with one of the types of neuroaxial or regional analgesia.*

· Early resumption of enteral nutrition for rapid rehabilitation for all patients operated for complicated forms of chronic pancreatitis [202–205].

Grade of Recommendation: B. Evidence level: 2.

Comments: *Oral intake of water up to 1000 ml/day at ongoing infusion therapy the day after*

surgery; after 2 days — increase in the volume of drinking fluid to 1500 ml along with decrease in the intravenous infusion volume, beginning of enteral nutrition; complete cancellation of infusion therapy, enteral nutrition.

• Early removal of catheters (central venous, urinary) and abdominal drains is recommended for all patients operated for complicated forms of chronic pancreatitis [202–205].

Grade of Recommendation: B. Evidence level: 2.

Comments: *Prolonged nasogastric intubation in the postoperative period is associated with high risk of gastroesophageal reflux, the development of pneumonia and atelectasis, delay in the recovery of gastrointestinal peristalsis [205] as a result it should not be used routinely in the postoperative period. Nasogastric tube installed for decompression of the upper gastrointestinal tract intraoperatively should be removed at the end of anesthesia, in rare cases (at the risk of developing gastrostasis) — in the first postoperative day. Removal of drainage from the abdominal cavity — for 4–5 postoperative days with the volume of discharge under 100 ml and the absence of 2-fold increase of amylase in it. If there are signs of pancreatic fistula, the drainage tube is not removed until the discharge is completely stopped.*

• All patients operated for complicated forms of chronic pancreatitis are recommended to administer the prophylactic dose of heparin in 12 hours prior to surgery and for up to 4 weeks after surgery in order to prevent thromboembolism [202–205].

Grade of Recommendation: B. Evidence level: 2.

Comments: *Long-term operations increase the risk of thromboembolism, so almost all patients when planning extensive operations on the pancreas are shown the prevention of deep vein thrombosis. Mechanical prevention of thrombosis (elastic and dynamic compression) is recommended for all hospitalized patients [205].*

5. Prevention and dispensary observation, medical indications and contraindications for prevention methods

Prevention of CP is based on extrapolation of data from cohort epidemiological studies, according to the results of which it can be assumed that the restriction of alcohol intake and tobacco smoking (categorical ban in patients with acute pancreatitis or established diagnosis of CP) may be a factor reducing the risk of progression of CP. In persons with symptomatic cholelithiasis, attacks of chronic calculous cholecystitis and biliary pancreatitis by preventing subsequent attacks of pancreatitis, elective cholecystectomy can be considered.

Empirical recommendations on dietary prophylaxis, the need to abandon almost all types of food, including coffee, chocolate, fats of any origin today are not scientifically based. It is possible (since not enough has been studied) that other factors associated with nutrition may be more significant for provoking an exacerbation of CP — obesity, overeating and hypokinesia after eating (with the development of high intra-abdominal pressure), chronic deficiency of antioxidants in food, hypercholesterolemia, combined effect of dietary factors, ethanol and components of tobacco smoke, etc. At the same time, we must remember the reverse side of the coin, when some highly compliant patients scrupulously follow a strict diet in order to prevent repeated attacks of pancreatitis (these are, as a rule, persons without alcoholic history, non-smokers) and bring themselves to nutritional deficiency with multivitamin deficiency, kwashiorkor, anemia, etc.

• Thus, based on the results of a number of experimental, epidemiological and pilot studies, empirical long-term experience to all patients with CP in order to prevent exacerbations of the disease, the following measures for lifestyle modification can be recommended: fractional nutrition (4–5 times per day, in uniform portions with the same proportion of fat-containing foods in the diet), refusal to overeat; creating a balanced diet with a restriction of saturated fats and cholesterol; including in the diet a sufficient amount of dietary fiber (vegetable fiber); sufficient physical activity; eating a variety of foods low in saturated fats and cholesterol (unrefined vegetable fats are somewhat limited only in overweight people); choosing a diet with a sufficient amount of dietary fiber, contained in cereal products, vegetables and fruits; balance between the amount of food taken and physical activity (to stabilize weight with aiming for ideal body mass age-adjusted) [202–204].

Grade of Recommendation: C. Evidence level: 5.

• All patients suffering from CP are advised to completely stop drinking alcohol in order to reduce the frequency of exacerbations and mortality *[24, 90, 206].*

Grade of Recommendation: C. Evidence level: 4.

Comments: *Stop of alcohol intake reduces the symptoms of CP, primarily reducing/completely relieving pain, slowing the development of exocrine pancreatic insufficiency [24, 90, 206].*

• All patients suffering from CP are advised to quit smoking completely in order to reduce pain and prevent the development of complications of CP [92].

Evidence level: 5,Grade of recommendation: C.

Comments: *All patients with CP are advised to quit smoking as significant and independent factor in the CP development [92].*

• Patients with gallstone disease in order to prevent attacks of biliary pancreatitis are recommended to undergo surgical treatment: cholecystectomy, endoscopic choledocholithoextraction [203].

Grade of Recommendation: C. Evidence level: 5.

• Dispensary observation by local physician, general practitioner or gastroenterologist at the place of residence is recommended after surgical treatment with comprehensive examination 1 time per year for patients who have undergone invasive interventions for chronic pancreatitis [38, 56, 61].

Grade of Recommendation: C. Evidence level: 5.

For effective primary prevention of CP the concept of total dispensary observation of the population may be effective in order to timely identify the pathology of the biliary tract, hyperlipidemia, stigmata of latent alcohol abuse, etc. However, so far in no country in the world has such an idea found practical application, since its implementation is worth a lot of material costs. The answer about the expediency of such tactics can be given by pharmacoeconomic studies, but to expect their initiation, taking into account the growing, but relatively low frequency of CP in the population should be recognized as unrealistic for the time being.

6. Organization of medical care

Stages of medical care

Outpatient and polyclinic stage — the identification of persons with suspected CP, the prescription of diagnostic manipulations, the diagnosis of CP, the prescription of conservative therapy followed by dynamic observation. With the ineffectiveness of conservative therapy — referral for surgical treatment.

Stationary stage

In the inpatient treatment of patients with CP, a three-level system of medical care should be implemented.

Levels of inpatient care for the population

The first level is medical organizations that have in their structure units that provide the population with primary health care and/or specialized (with the exception of high-tech) medical care **within the municipality.**

The scope of medical care at the first level: conservative therapy of CP during the relapse period, referral to second-level institutions to perform palliative interventions in case of biliary hypertension, duodenal obstruction, additional treatment/rehabilitation of patients after operations performed in the 2nd and 3rd level hospitals. Patients with urgent complications requiring specialized high-tech care (X-ray endovascular stopping portal or arterial bleeding, stenting of pancreatic ducts), are referred to the 3rd level hospitals, bypassing the 2nd level.

Indications for hospitalization in first-level hospital — a clinical picture of exacerbation of CP, laboratory, ultrasound diagnostics, conservative therapy.

The grounds for discharge from the hospital of the first level are the copulation of the pain syndrome, the normalization of laboratory parameters (general amylase, pancreatic amylase, urine amylase, leukocyte level).

The second level is medical organizations that have departments and (or) centers that provide specialized (with the exception of high-tech) medical care to the population **of several municipalities** in their structure, as well as emergency medical care hospitals.

The scope of medical care at the second level: palliative operations for obstruction of the biliary tract, subcompensated and decompensated duodenal obstruction, transfer from the first-level hospital in the development of conditions requiring treatment in intensive care and surgical intervention (bleeding from PA).

Indications for hospitalization in a second-level hospital: the presence of a symptom complex of bilabial obstruction, subcompensated, decompensated duodenal stenosis, pronounced persistent pain syndrome.

The grounds for discharge from the second-level hospital are clinical and laboratory signs of relief of mechanical jaundice after intervention, restoration of evacuation from the stomach, relief of pain.

The third level is medical organizations that have in their structure units that provide the population with high-tech medical care associated with technically complex interventions, with a high risk of perioperative complications that require joint work of diagnostic, surgical, endoscopic, anesthesiology and resuscitation, X-ray endovascular services, which should be available around the clock. This condition may be is implemented only in high-volume centers.

Indications for hospitalization in a third-level hospital — complicated course of CP (persistent pain syndrome that is not amenable to drug therapy; ductal hypertension of the pancreas due to MPD stones or strictures of the pancreatic duct; postnecrotic pancreatic cysts of the pancreas; mechanical jaundice caused by compression of terminal CBD; portal hypertension with bleeding from varicose veins due to compression of the portal vein confluence; persistent violation of the passage of food through the duodenum; PA arteries pool of the celiac trunk and superior mesenteric artery, suspected malignancy,

external and internal fistulas of the pancreas), requiring surgery in the volume of resection of the pancreas, PDR, distal resection of the pancreas, endovascular interventions.

The grounds for discharge from the third-level hospital are a satisfactory condition in the postoperative period, the absence of complications [202, 204].

Tactics of managing patient with CP for general practitioner and gastroenterologist

The tactics of managing a patient with CP are based on several important components:

1. Determination of the diagnosis of CP (i.e. confirmation or exclusion of CP, causing difficulties in the early stages of the disease);
2. Attempt to determine the etiology of CP (since the etiotropic treatment is most effective);
3. Determination of the stage of CP (which determines the choice of treatment tactics and affects the prognosis);
4. Diagnosis of pancreatic insufficiency (is the basis for choosing a scheme of enzyme replacement therapy and insulin therapy, doses of drugs or recognition of the need for surgical treatment);
5. Development of a treatment plan (in some cases, a joint decision with surgeons, endoscopists, endocrinologists);
6. Determination of the prognosis, taking into account the initial situation and the chosen medical tactics.

The diagnosis of "definite CP" (Algorithm 1) is established using highly informative radiological methods according to morphological signs in combination with clinical manifestations (at indecisive conclusion of ultrasound — at least CT). In the event that neither ultrasound nor CT give confirmation of the diagnosis, the patient can be observed and treated with a probable diagnosis of CP. So, if the diagnosis of CP is convincingly proven, on the first an attempt at an etiotropic (most effective) effect is carried out. First of all, this applies to etiological forms that require timely and specific effects — at AIP — corticosteroids for systemic use, in obstructive pancreatitis — surgical or endoscopic decompression, etc. In the presence of exocrine pancreatic insufficiency, it is advisable to determine its type — primary (with a decrease in elastase-1 if the conditions of collection are met) or secondary (with a normal level of elastase), which will determine the duration enzyme replacement therapy. The duration of pancreatin capsules** in secondary pancreatic insufficiency intake is determined by the period of resolution of symptoms, the possibility of identification and eliminating secondary causes of insufficiency (e.g. small intestinal bacterial overgrowth syndrome). In case of relapse of steatorrhea after discontinuation or reduction of the dose of pancreatin** despite the normal values of fecal elastase-1, lifelong enzyme replacement therapy is necessary. For a patient with low values of fecal elastase-1 in the absence of condition for false-positive result pancreatin lifelong enzyme replacement therapy is indicated. In persistent pain resistant to combined pharmacotherapy using pancreatin**, analgesics, pregabalin** for 3 months, it is advisable to discuss the patient in team-based discussion together with surgeons and endoscopists for endoscopic or surgical treatment. When prescribing narcotic analgesics, high risk of dependence develops, which dictates a more compressed time frame to decide on the possible need for endoscopic and/or surgical treatment.

If it is impossible for various reasons to carry out adequate morphological verification of CP, as well as the fact that the most common method for assessing the state of the pancreatic parenchyma in Russia at the present time is ultrasound, in some patients the diagnosis of "chronic pancreatitis" is probable or possible depending on the history data and clinical signs (Algorithm 2). A similar situation develops with insufficient CT data, and in some cases even EUS, in the diagnosis of CP (uncertain, probable CP or possible CP). In the presence/suspicion of exocrine pancreatic insufficiency, it is also advisable to determine its type — primary (with a decrease in elastase-1) or secondary (with a normal level of elastase), which will determine the duration of enzyme replacement therapy and allow us to assert with greater confidence the presence of CP (a combination of inconclusive radiological criteria and pancreatic insufficiency). Duration of intake of pancreatin capsules** in secondary pancreatic insufficiency is also determined by the period of resolution of symptoms, the possibility of revealing and eliminating secondary causes of insufficiency (for example, the small intestinal bacteria overgrowth syndrome). Due to the lack of confidence in the "pancreatic" type of diabetes, the choice of hypoglycemic agent should be decided together with endocrinologist. In the absence of the effect of conservative techniques aimed at relieving pain, in contrast to the situation of "definite CP", before consulting with a surgeon, it is advisable, first of all, to clarify the diagnosis of CP using reliable methods for assessing the pancreatic morphology (EUS, CT, MRCP).

7. Additional information (including factors affecting the outcome of the disease or condition)

Factors affecting the outcome of surgical treatment of chronic pancreatitis

Up to 20 % of operated patients are not satisfied with the result of surgical treatment [205]. This primarily concerns the recurrence or persistence of pain after surgery [205, 207]. The factors affecting

the efficacy of surgery are not fully understood. One of them is the volume of resection of the pancreatic head. As a result of meta-analysis conducted in 2016, which included 323 patients after resection-draining interventions on the pancreas in various modifications, it was noted that in all cases surgical treatment had a satisfactory result [208, 209]. However, none of the publications included in the meta-analysis described a method for objectively estimating the volume of resection of the pancreatic head.

Another possible factor affecting the outcome of treatment is the duration of surgery. Surgery for CP performed in the early stages of the disease (up to 3 years from the initial manifestation) leads to better long-term results. Recently, there have been isolated single-center studies noting the advantage of surgical treatment of CP in the early stages from the initial manifestation of the disease (up to 3 years) [208, 209].

Prognosis of the course of CP

Currently, there is no prognostic system of the course of chronic pancreatitis approved by the professional community. Large cohort studies and meta-analyses are needed to more accurate identification of the factors that affect the outcome of CP.

Obviously, when predicting the course of CP, it is necessary to rely on the data of the physical state of the patient (BMI), the influence of toxic factors (alcohol, smoking), laboratory test data (the level of glycosylated hemoglobin of the blood, C-reactive protein, albumin), the state of the pancreas (post-necrotic cysts and stones), the presence of biliary strictures.

For an objective assessment of the patient's condition in dynamics, questionnaires are widely used, such as the visual-analog scale (VAS) (appendix G8), numeric rating scale (NRS) (appendix G9), as well as questionnaires for assessing the quality of life (QOL) SF-36 (appendix G10), QLQ -C30 (appendix G10) [209–211].

To slow down fibrous and inflammatory processes in the pancreas and improve the condition of patients, lifestyle modification is necessary, including complete rejection of alcohol, compliance with dietary recommendations, and adequate [201].

Criteria for assessing the quality of medical care

№	Quality criteria	UDD	CID
1	Determination of the activity of serum alpha-amylase in exacerbation of pancreatitis — completed on the first day after hospitalization of the patient	2	C
2	Determination of the activity of serum alpha-amylase in relapse of pancreatitis at least 2 times in dynamics during single hospitalization	2	B
3	Abdominal ultrasound performed	5	C
4	Examination by surgeon in the presence of persistent pain syndrome or complications of chronic pancreatitis	2	B
5	Relief of abdominal pain achieved	2	B
6	CT with intravenous contrast to verify the diagnosis of «chronic pancreatitis» in the primary diagnosis of the disease (The study was performed according to the pancreatic protocol with iv contrast enhancement and description of all 4 phases of contrast) *(for 3rd level medical organizations)*	3	C
7	MRI / MRCP in patients with chronic pancreatitis and newly diagnosed cystic formation of the pancreas *(for 3rd level medical organizations)*	2	B
8	Endoscopic ultrasound examination of the pancreatobiliary zone with suspected obstructive etiology of pancreatitis (clinical or radiological signs of pancreatic or biliary hypertension, endoscopic signs of changes in the large duodenal papilla) *(for 3rd level medical organizations)*	2	B
9	Determination of the level of IgG_4 in the blood serum with suspected autoimmune etiology of chronic pancreatitis (diffuse or focal enlargement of the pancreas according to CT or MRI) *(for 3rd level medical organizations)*	2	B
10	Pancreatin form** for replacement therapy of exocrine pancreatic insufficiency should be capsules	1	A
11	For replacement therapy, the prescription of pancreatin** in capsules at a dose of 25-40 thousand IU lipase for the main meal and 10-25 IU lipase for an intermediate meal, with a multiplicity of at least 5 times / day.	1	A
12	Monitoring the efficacy of replacement therapy according to clinical indicators of trophological status after 6 months from onset of replacement therapy (for the outpatient stage of treatment)	2	B
13	Prevention of infectious complications with broad-spectrum antibacterial drugs was carried out 30 minutes before surgery (in the absence of medical contraindications)	2	B
14	A pathologic examination of the surgical material of the pancreas was performed (during surgical intervention)	5	C

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Appendix A2. Methodology for the development of clinical guidelines

The proposed recommendations are aimed at bringing to practitioners modern ideas about the etiology and pathogenesis of CP, to acquaint them with the currently used algorithm for the diagnosis and treatment of CP.

The target audience of these clinical guidelines:
1. Doctors-gastroenterologists
2. Doctors-therapists
3. General practitioners (family medicine)
4. Endoscopists
5. Surgeons

Levels of evidence (LE) Rating Scale for Diagnostic Methods (Diagnostic Interventions)

LE	Explanation
1	Systematic reviews of reference-controlled studies or systematic review of randomized clinical trials using meta-analysis
2	Individual reference control studies or separate randomized clinical trials and systematic reviews of studies of any design, with the exception of randomized clinical trials, using meta-analysis
3	Studies without sequential control by the reference method or studies with a reference method that is not independent of the method under study or non-randomized comparative studies, including cohort studies
4	Incomparable studies, description of a clinical case
5	There is only a justification for the mechanism of action or the opinion of experts

Scale for assessing levels of evidence (LE) for methods of prevention, treatment and rehabilitation (preventive, curative, rehabilitation interventions)

LE	Explanation
1	Systematic review of randomized clinical trials using meta-analysis
2	Individual randomized clinical trials and systematic reviews of studies of any design, with the exception of randomized clinical trials, using meta-analysis
3	Non-randomized comparative studies, including cohort studies
4	Non-comparative studies, description of a clinical case or a series of cases, case-control study
5	There is only a justification for the mechanism of action of the intervention (preclinical studies) or the opinion of experts

Scale for assessing the grades of recommendations (GR) for methods of prevention, diagnosis, treatment and rehabilitation (preventive, diagnostic, therapeutic, rehabilitative interventions)

GR	Explanation
A	Strong recommendation (all outcomes considered are important, all studies are of high or satisfactory methodological quality, their conclusions on outcomes of interest are consistent)
B	Conditional recommendation (not all outcomes considered are important, not all studies are of high or satisfactory methodological quality, and/or their conclusions on outcomes of interest are not consistent)
C	Weak recommendation (lack of evidence of good quality (all outcomes considered are unimportant, all studies have low methodological quality and their conclusions on outcomes of interest are not consistent)

Procedure for updating clinical guidelines

The mechanism for updating clinical guidelines provides for their systematic updating — at least once every three years, as well as when new data appear from the standpoint of evidence-based medicine on the diagnosis, treatment, prevention and rehabilitation of specific diseases, the presence of justified additions / comments to previously approved CD, but not more than 1 time in 6 months.

Appendix A3. Reference materials, including the correspondence of indications for use and contraindications, methods of use and doses of drugs, instructions for use of the medicinal product

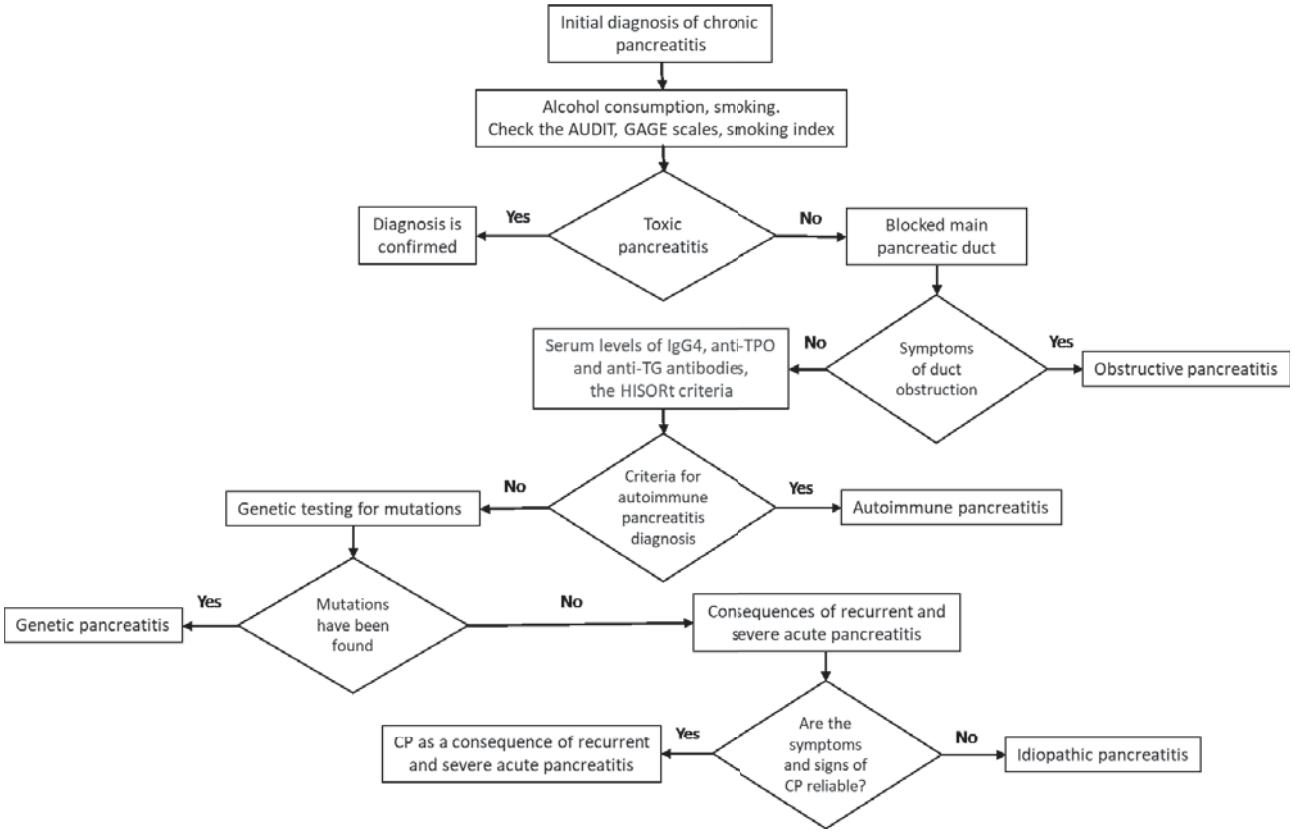
These clinical guidelines are developed taking into account the following regulatory and legal documents:

1. Federal Law of the Russian Federation dated November 21, 2011 No. 323-FZ "On the Basics of Protecting the Health of Citizens in the Russian Federation".

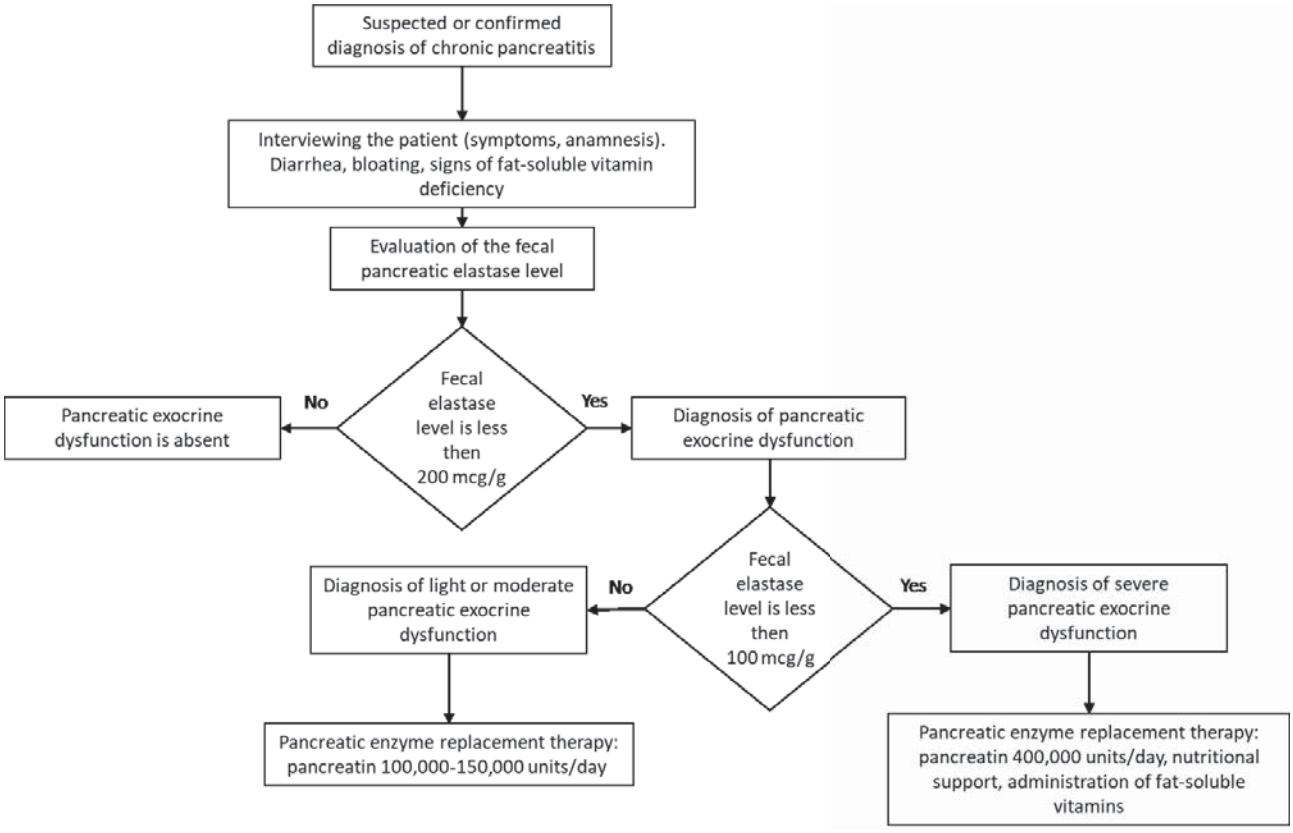
2. Order of the ministry of Health of the Russian Federation dated October 13, 2017 No. 804n (as amended on 12.07.2018) "On Approval of the Nomenclature of Medical Services".

3. Order of the ministry of Health of the Russian Federation dated 05.03.2020 No. 148n "On Amendments to Section II "Nomenclature of Medical Services" of the nomenclature of medical services approved by the Order of the ministry of Health of the Russian Federation dated October 13, 2017 No. 804n".

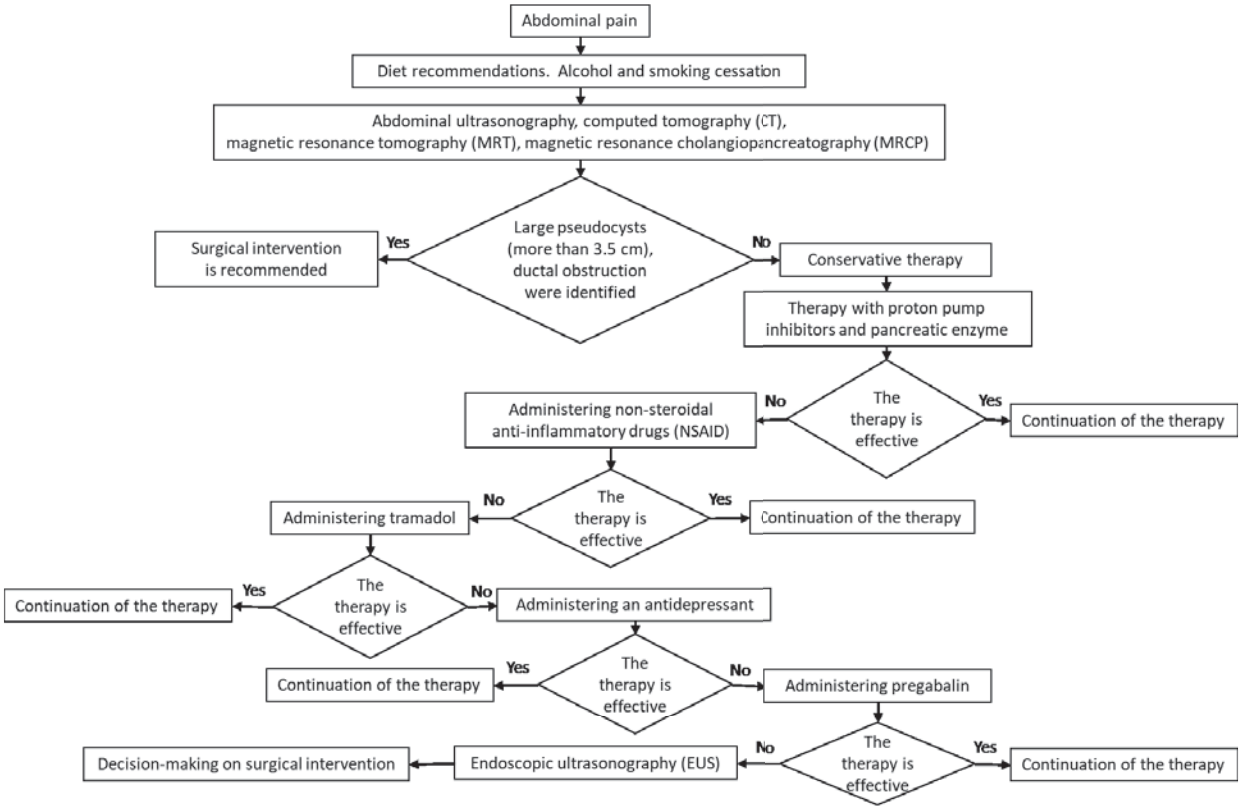
Appendix B. Algorithms of the doctor's actions



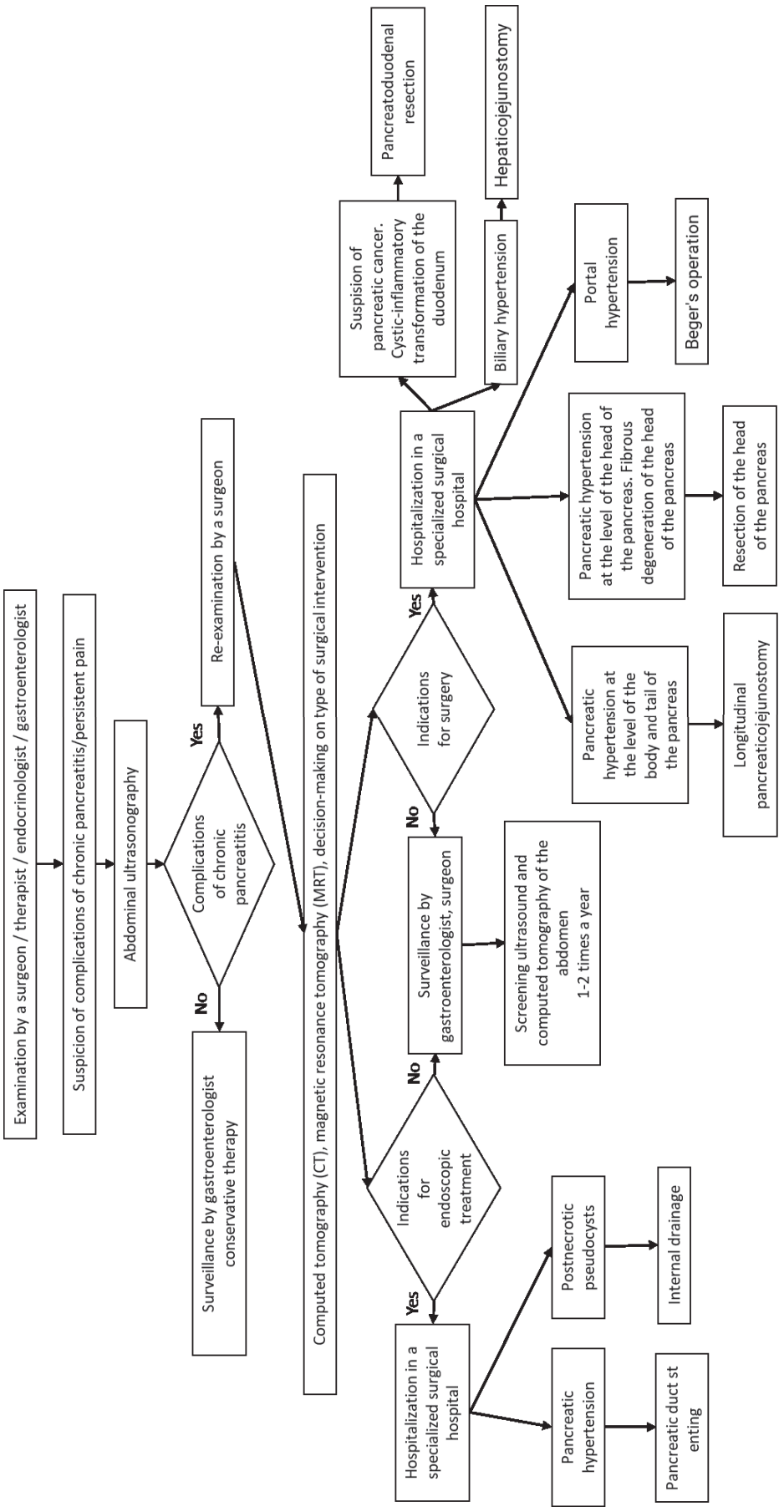
Algorithm 1. Tactics of managing a patient with a proven diagnosis of "chronic pancreatitis"



Algorithm 2. Tactics of managing a patient with a probable diagnosis of "chronic pancreatitis"



Algorithm 3. Tactics of examination and treatment of a patient with chronic pancreatitis with dominant abdominal pain



Algorithm 4. Tactics of the surgeon for CP

Appendix B "Patient Information"

If pancreatitis is suspected, a comprehensive examination is necessary in order to establish an accurate diagnosis (in the first two to three years of the disease, many laboratory and instrumental indicators may be within normal limits, and clinical signs are not characteristic only of this disease). Treatment of chronic pancreatitis involves: dieting, analgesic therapy, taking vitamins, enzyme replacement therapy, treatment of diabetes mellitus and other endocrine disorders, timely treatment of cholelithiasis.

Appendix G1–G11. Rating scales, questionnaires and other assessment tools of the patient's condition given in the clinical guidelines

Appendix G1. AIP Diagnostic Criteria (HISORt System)

The HISORt system includes the following groups of features [61]:

- morphological features ("Histology") — periductal lymphoplasmacytic infiltrate with obliterating phlebitis, fibrosis in the form of vortices, and/or lymphoplasmacytic infiltrate with fibrosis in the form of vortices and a large number of IgG_4-positive cells ≥10 in the field of view (vf);
- data of radiological diagnostic methods ("Imaging"): diffuse increase in the pancreas with a delayed accumulation of contrast in the form of a "rim", diffuse unevenness of the main pancreatic duct (MPD);
- Serological markers ("Serology"): an increase in serum IgG_4 levels (8–140 mg%);
- involvement of other organs ("Other organ involvement"): strictures of the bile ducts, fibrosis of the retroperitoneal tissue, damage to the salivary / lacrimal glands, mediastinal lymphadenopathy;
- response to treatment ("Response to steroid therapy"): the positive effect of the prescription of 30–40 mg / day of prednisolone for 1 month.

Diagnostic criteria give the following levels of probability of diagnosing AIP:

Level A: Typical histological features.

One or more of the following symptoms are present:

- a tissue area with characteristic features of lymphoplasmacytic sclerosing pancreatitis;
- ≥10 IgG_4-positive cells in vf against the background of lymphoplasmacytic infiltration.

Level B: Typical Laboratory and Instrumental Data.

Presence of all signs:

- diffuse increase in the pancreas according to computed and magnetic resonance imaging (CT, MRI) with delayed contrast enhancement and the presence of a rim ("capsule");
- diffuse unevenness of the lumen of the MPD in endoscopic retrograde pancreatocholangiography (ERCP);
- Increased serum IgG_4 levels.

Level C: Positive Response to Steroid Hormones.

Presence of all signs:

- exclusion of all other causes of pancreatic lesions;
- an increase in serum IgG_4 levels or damage to other organs, confirmed by the detection of a large number of IgG_4-positive cells;
- disappearance / significant improvement of pancreatic or extrapancreatic changes against the background of steroid therapy.

Appendix G2. Rosemont pancreatobiliary EUS Diagnostic Criteria

Parenchymal signs of CP					
Sign	Definition	Criteria		Rank	Histological correlation
		Main	Additional		
Hyperechoic foci with shade	Echogenic structures ≥2 mm in length and width with shadow	Main A		1	Calcinosis of the parenchyma
Lobularity	Well-demarcated structures of ≥5 mm in size with a hyperechoic rim and a relatively hypoechoic center			2	Unknown
With cellularity	Availability of adjacent ≥3 slices	Main B			
Without cellularity	Presence of non-contiguous lobules		Yes		
Hyperechoic foci without shadow	Echogenic structures focuses ≥2 mm in length and width without shadow		Yes	3	Unknown
Cysts	Anechoic, rounded / elliptical structure, with or without lintels		Yes	4	Pseudocyst
Heaviness	Hyperechoic strands ≥3 mm in length in at least 2 different directions relative to the plane of image		Yes	5	Unknown
Ductal signs of CP					
Stones in the MPD	Echogenic structure(s) in MPD with acoustic shadow	A		1	Stones
MPD contour unevenness	Unevenness or irregularity contour and tendency to expand		Yes	2	Unknown
Expansion of lateral ducts	≥3 anechoic cylindrical structures, each ≥1 mm wide, running from the MPD		Yes	3	Expansion of lateral ducts
Expansion of lateral ducts	≥3 anechoic cylindrical structures, each ≥1 mm wide, running from the MPD		Yes	3	
Expansion of the MPD	≥3.5 mm in body or > 1.5 mm in tail		Yes	4	Expansion of the MPD
Hyperechogenicity of the MPD wall	Echogenic structures with clear boundaries > 50 % of MPD in the body and tail		Yes	5	Duct fibrosis

Criteria for the diagnosis of CP according to EUSPBA data:
Definite CP
- 1 main A sign (+) ≥3 additional features
- 1 main A sign (+) main B sign
- 2 Main A signs

Presumptive CP*
- 1 main A feature (+) <3 additional signs
- 1 main B feature (+) ≥3 additional features
- ≥5 additional features (any)

Possible CP**
- 3–4 additional features, absence of main features
- One main B sign or combined with <3 additional features

Norm
- <2 additional features***, absence of main features

Note: * Diagnosis of CP by EUS should be carried out in appropriate clinical settings. ** Requires confirmation by additional imaging (ERCP, CT, MRI or pancreatic functional tests — PFT). ******With the exception of cysts, dilatation of the MPD, hyperechoic lesions without a shadow, dilatation of the lateral ducts.

With the exception of cysts, dilatation of MPD, hyperechoic foci without shadow, dilatation of lateral ducts.

Appendix G3. Classification of ERPG data in CP

Table 3. Classification of pancreatograms in CP

Terminology	MPD	Modified side branches	Additional symptoms
Norm	Norm	No	
Questionable data	Norm	<3	
Easy CP	Norm	≥3	
Moderately severe CP	Changed	>3	
Severe CP	Changed	>3	One or more: large cavity, obstruction, filling defects, pronounced expansion or unevenness

Appendix G4. Classification of the severity of CP according to CT and ultrasound data

Table 4. Cambridge Classification of CP by CT and Ultrasound (81)

Severity	Changes
Norm	MPD <2 mm Normal size and shape of the pancreas Homogeneity of the parenchyma
Doubtful	One sign of the following: MPD 2–4 mm Slight enlargement (up to 2N) Heterogeneity of the parenchyma
Light	Two or more signs are necessary: MPD 2–4 mm Slight enlargement (up to 2N) Heterogeneity of the parenchyma
Moderately severe	Small cavities <10 mm Uneven diameter of ducts Focal acute pancreatitis Increased echogenicity of the duct wall Uneven contours
Heavy	See above + one or more signs: Large cavities (>10 mm) Significant enlargement of the gland (>2N) Filling defects inside ducts or stones Obstruction of ducts, strictures or pronounced unevenness of diameter Damage to neighboring organs

Appendix G5. Paddington Alcohol Test

Title in Russian: Paddington Alcohol Test

Original title (if any): The Paddington Alcohol Test

Source R. Patton, C. Hilton, M.J. Crawford, R. Touquet. The Paddington Alcohol Test: a short report. Alcohol and alcoholism. 2004;39(3):266–8.

Type (underline):

- Rating scale
- Index
- Questionnaire

Purpose: Evaluation of alcohol consumption

Content

Paddington Alcohol Test

1. Do you drink alcohol?
Yes – go to step 2.
No
2. Almost most people sometimes drink more than usual, how much maximum could you drink on such a day?

	Standard drinks	**Vodka (ml) 40 %**	**Fortified wine (ml) 17–20 %**	**Dry wine 11–13 %**	**Beer (bottle) 5 %**
(0)	1 or 2	30–60	75–150	75–150	250 ml–1 b
(1)	3 or 4	90–120	225–300	300–400	1.5–2 b.
(2)	5 or 6	150–180	375–450	500–600	2.5–3 b.
(3)	7 or 8	210–240	525–600	700	3.5–4 b.
(4)	10 or more	300 and more	750 and more	1000 and more	5 b. and more

3. How often do you consume 8/6 (for men and women, respectively) standard drinks of alcoholic beverages per day:
· once a week or more often = PAT status +
· or, if less frequently:
· at least once a month = PAT status +
· less than once a month = PAT status – (go to 4)
4. Do you think this examination by your doctor is related to alcohol intake?
Yes = PAT status +
No = PAT status –

Key: The Paddington Alcohol Test (PAT) [212] takes little time and is comparable in sensitivity to AUDIT, it is considered positive (alcohol abuse), with a positive answer to the 3rd and/or 4th question.

Appendix G6. Key antrometric indicators of nutritional status [173]

Index	**Norms**	
	Men	**Women**
TTS, mm	12,5	16,5
SC, cm	26–29	25–28
WMD, cm	25,3	23,2

Note. The circumference of the muscles of the shoulder is determined by the formula

WMD (cm) = OP (cm) – 0.314 x FGST (mm)

SC – shoulder circumference, TTS – thickness of triceps skinfolds

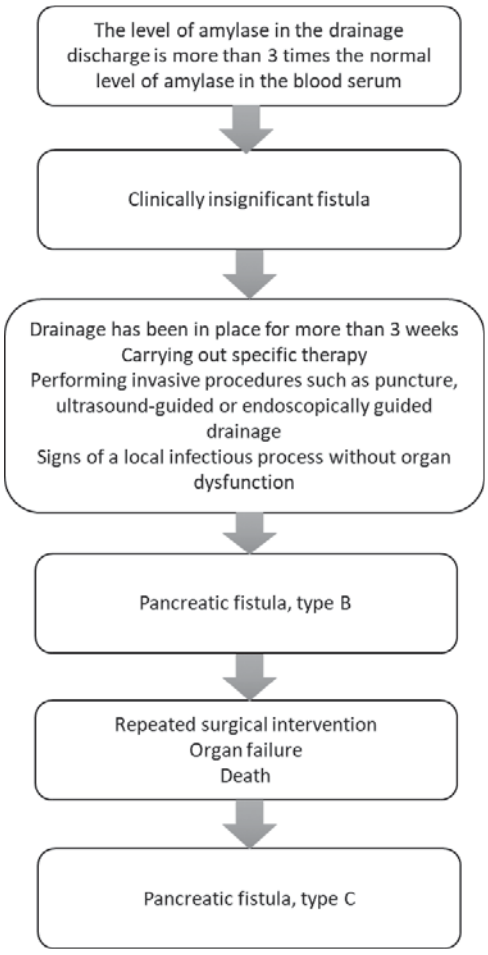
Nutritional status according to TTS and WMD:

Normal	**90–100 %**
Mild impairment	90–80 % of the norm
Violation of moderate severity	80–70 % of normal value
Severe impairment	<70 % of the norm

BMI Nutrition Status

Classification	**BMI (kg/m²)**	**Risk of comorbidities**
Hypotrophy 3 grade	below 15.0	Extremely high
Hypotrophy 2 grade	15.0–16.9	Taut
Hypotrophy 1 grade	17.0–18.4	High
Normal MT	18.5–24.9	Usual
Excess MT	25.0–29.9	Taut

Appendix G7. Diagnostic criteria for pancreatic fistulas after pancreatic surgery, *ISGPF2017*



Appendix G8. Visual Analog Scale (VAS)

Title in Russian: Visual Analog Scale (VAS)

Original title (if any): Visual analogue scale (VAS)

Source (official website of the developers, publication with validation): http://img.medscape.com/article/742/580/VAS.pdf

Type (underline):
- Rating scale
- Index
- Questionnaire

Purpose: Assessment of pain levels

Contents (template):

Key (interpretation): Each centimeter on the scale corresponds to one point. So pain from 0 to 2 points is classified as weak, from 2 to 4 — moderate, from 4 to 6 — strong, from 6 to 8 — the strongest, up to 10 cm — unbearable.

Explanation: The visual analog scale is a segment of 10 cm in length, its starting point corresponds to the absence of pain — "there is no pain", and the end is the most pronounced pain sensation "unbearable pain". The patient is asked to choose a point on the segment that corresponds to the intensity of the pain that he is experiencing at the present time. The distance from the segment to the marked point is measured and rounded to the whole.

Appendix G9: Numeric rating scale

Original title (if any): Numeric rating scale (NRS)

Source (official website of the developers, publication with validation): https://www.sciencedirect.com/topics/medicine-and-dentistry/numeric-rating-scale

Type (underline):
- Rating scale
- Index
- Questionnaire

Purpose: Assessment of pain levels

Contents (template):

Please rate the intensity of the pain you are currently experiencing										
0	1	2	3	4	5	6	7	8	9	10
no pain					Moderate pain					Very severe pain

Digital rank scale of pain in graphic form.

Key (interpretation): THE CRS consists of a sequential series of numbers from 0 to 10. Patients are asked to estimate the intensity of pain with numbers: 0 — no pain, 5 — moderate pain and 10 — the most severe pain that can be imagined

Explanation: An alternative to VAS is the digital (digital rank) pain scale (CRS: NRS). The advantage of the CRS is the ability to use it both graphically and orally (including during a telephone survey)

Appendix G10. Quality of Life Assessment Questionnaires

Original title: Short form 36 (SF-36)

Source (official website of the developers, publication with validation): https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form.html

M. Wehler, U. Reulback, R. Nichterlein, et al. Health-related quality of life in chronic pancreatitis: a psychometric assessment. Scan J Gastroenterol 2003; 38 :1083–9 [213].

Type (underline):
- Rating scale
- Index

- Questionnaire
Purpose: Quality of Life Assessment
Contents (template):

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- ○ 1 - Excellent
- ○ 2 - Very good
- ○ 3 - Good
- ○ 4 - Fair
- ○ 5 - Poor

---

2. **Compared to one year ago**, how would you rate your health in general **now**?

- ○ 1 - Much better now than one year ago
- ○ 2 - Somewhat better now than one year ago
- ○ 3 - About the same
- ○ 4 - Somewhat worse now than one year ago
- ○ 5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
14. **Accomplished less** than you would like	○ 1	○ 2
15. Were limited in the **kind** of work or other activities	○ 1	○ 2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	○ 1	○ 2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	○ 1	○ 2
18. **Accomplished less** than you would like	○ 1	○ 2
19. Didn't do work or other activities as **carefully** as usual	○ 1	○ 2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- ○ 1 - Not at all
- ○ 2 - Slightly
- ○ 3 - Moderately
- ○ 4 - Quite a bit
- ○ 5 - Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

- 1 - None
- 2 - Very mild
- 3 - Mild
- 4 - Moderate
- 5 - Severe
- 6 - Very severe

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- 1 - Not at all
- 2 - A little bit
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
24. Have you been a very nervous person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
25. Have you felt so down in the dumps that nothing could cheer you up?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
26. Have you felt calm and peaceful?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
27. Did you have a lot of energy?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
28. Have you felt downhearted and blue?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
29. Did you feel worn out?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
30. Have you been a happy person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
31. Did you feel tired?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

- ○ 1 - All of the time
- ○ 2 - Most of the time
- ○ 3 - Some of the time
- ○ 4 - A little of the time
- ○ 5 - None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	○ 1	○ 2	○ 3	○ 4	○ 5
34. I am as healthy as anybody I know	○ 1	○ 2	○ 3	○ 4	○ 5
35. I expect my health to get worse	○ 1	○ 2	○ 3	○ 4	○ 5
36. My health is excellent	○ 1	○ 2	○ 3	○ 4	○ 5

Key (interpretation): http://abdugaliev.ru/proj/medcalc/sf36__

Explanations: The generally accepted indicator of the patient's condition, which allows to objectify the subjective sensations of the patient, is the quality of life (QOL). QOL is determined using questionnaires developed in the course of special studies. The questionnaire was created for patients with chronic diseases and has no nosological specificity. QLQ questionnaire C30 was originally created to assess the quality of life of cancer patients, but studies have shown the possibility of its use among patients suffering from CP [213].

Appendix G11. Questionnaires for assessing the quality of life.

Original title (if any): EORTC QLQ-C30

Source (official website of the developers, publication with validation): https://qol.eortc.org/

D. Fitzsimmons, S. Kahl, G. Butturini, et al. Symptoms and quality of life in chronic pancreatitis assessed by structured interview and the EORTC QLQ-C30 and QLQ-PAN26. Am J Gastroenterol. 2005;100:918–26.

Type (underline):

- Rating scale
- Index
- **Questionnaire**

Purpose: Quality of Life Assessment

Contents (template):

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Key (interpretation): https://www.eortc.org/app/uploads/sites/2/2018/02/reference_values_manual2008.pdf

Explanation: The QLQ C30 questionnaire was originally created to assess the quality of life of cancer patients, but studies have shown the possibility of its use among patients suffering from CP.

Appendix G12. Nomenclature of medical services used in the diagnosis and surgical treatment of chronic pancreatitis

as amended by the Order of the ministry of Health of Russia dated 16.04.2019 No. 217n, with amendments,

Laboratory diagnostics:

B03.016.002 General (clinical) blood test

B03.016.003 General (clinical) blood test detailed

B03.016.004 Biochemical general therapy blood test

B03.016.005 Blood test for the assessment of lipid metabolism disorders biochemical

B03.016.006 General (clinical) analysis of urine

B03.016.010 Coprologic study

B03.016.017 Complex determination of the concentration of fatty acids in the blood

B03.027.027 Complex of studies for the diagnosis of malignant neoplasms of the pancreas

A09.05.045 Determination of amylase activity in the blood

A09.05.046 Determination of alkaline phosphatase activity in blood

A09.05.180 Determination of pancreatic amylase activity in the blood

A09.28.027 Determination of alpha-amylase activity in urine

A09.30.009 Determination of amylase activity in peritoneal fluid

Instrumental diagnostics:

B03.052.001 Complex ultrasound examination of internal organs

A06.30.005 Computed tomography of the abdominal organs

A06.30.005.002 Computed tomography of the abdominal organs and retroperitoneal space with intravenous bolus contrast-enhancement

A06.30.005.003 Computed tomography of the abdominal organs with intravenous bolus enhancement

A06.30.005.004 Spiral computed tomography of the abdominal organs with intravenous bolus enhancement, multiplanar and three-dimensional reconstruction

A06.30.008 Fistulography

A06.30.008.001 Computed tomography fistulography

A05.30.005 Magnetic resonance imaging of the abdominal organs

A05.30.005.001 Magnetic resonance imaging of the abdominal organs with intravenous contrast

A05.14.002 Magnetic resonance cholangiography

A05.15.001 Magnetic resonance imaging of the pancreas

A05.15.002 Magnetic resonance cholangiopancreatography

A03.16.001 Esophagogastroduodenoscopy

A03.16.002 Installation of a nasointestinal probe

A04.14.003 Endosonography of the pancreatobiliary zone

A04.16.003 Duodenal endosonography

Surgical and endoscopic treatment:

A16.15.010 Pancreatoduodenal resection

A16.15.010.002 Pancreatoduodenal resection with preservation of the pylorus

A16.15.010.003 Robotic pancreatoduodenal resection

A16.15.010.004 Robotic supporting sawmill pancreatoduodenal resection

A16.15.001.002 Endoscopic pancreatic resection

A16.15.001.003 Partial resection of the pancreatic head with pancreatoejunoanastomosis (Frey's operation)

A16.15.002 Suturing of pancreatic damage

A16.15.004 Cystoenterostomy

A16.15.006 Transduodenal sphincterovirsungoplasty

A16.15.007 Virsungoduodenostomy

A16.15.008 Longitudinal pancreatoeyenostomy

A16.15.009.001 Distal pancreatic resection with preservation Spleen

A16.15.009.002 Distal resection of the pancreas with splenectomy

A16.15.015 External drainage of pancreatic cysts

A16.15.015.001 Drainage of pancreatic cysts under control Ultrasound

A16.15.015.002 Transcatheter treatment of pancreatic cysts under ultrasonic testing control

A16.15.015.003 Occlusion of pancreatic cysts under control Ultrasound

A16.15.016 Occlusion of pancreatic fistulas

A16.15.016.001 Occlusion of external pancreatic fistulas

A16.15.016.002 Separation of internal pancreatic fistulas

A16.15.017 Excision of pancreatic cysts

A16.15.019 Imposition of pancreatic (cysto)euno-anastomosis

A16.15.020 Reconstructive interventions in chronic pancreatitis

A16.14.031.003 Choledochoyenoanastomosis

A16.14.032 Bile duct stenting

A16.14.032.001 Endoscopic virsungotomy

A16.14.032.002 Bile duct stenting under videoendoscopic control

A16.15.021 Endoscopic stenting of the main pancreatic duct

A03.16.002 Installation of a nasointestinal probe

A16.12.041.001 Endovascular occlusion by means of microspirals

A16.12.041.002 Endovascular occlusion of the aneurysm cavity by means of microspirals

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