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Practice Guidelines

Guidelines for the diagnosis and treatment of chronic pancreatitis in China (2018 edition)

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Chronic pancreatitis (CP) is a progressive inflammatory disease of pancreas that alters the organ's normal structure and functions. CP seriously affects the quality of life of patients and greatly increases the public medical burden of society. In recent years, the incidence of CP has increased worldwide. The concepts of etiology and therapies have been continuously updated. Clinical treatment guidelines for the disease have been issued in Japan, the United States and Europe. The Chronic Pancreatitis Group of China organized over 80 experts of Gastroenterology, Biliary and Pancreatic Surgery, Endocrinology, Radiology and Pathology to revise and update *the Chinese Guidelines for the Diagnosis and Treatment of Chronic Pancreatitis (*2012 *edition)*. The new guidelines are based on the latest medical evidence from China and other countries.

Definitions and terminology

CP is a progressive inflammatory disease of pancreas caused by genetic and environmental factors [1]. The pathological characters are the atrophy and destruction of pancreatic acinar cells and fibrosis. The main clinical manifestations are recurrent upper abdominal pain and pancreatic exocrine and endocrine insufficiency, accompanied by pancreatic duct stones, pancreatic duct stenosis, irregularity of the pancreatic duct and pancreatic pseudocysts.

Alcoholic CP is defined as an alcohol intake of $\geq$ 80 g/d for a male or 60 g/d for a female for at least two years in CP patients, excluding other causes [2].

Recurrent acute pancreatitis is defined as at least two episodes of acute pancreatitis with no change of pancreatic tissue and function during remission [3].

Hereditary CP is diagnosed when there are at least two first-degree relatives or three second-degree relatives with CP or recurrent acute pancreatitis in two or more generations in the family of a CP patient [4].

Idiopathic CP is defined as the absence of any known causes in CP patients.

Fatty diarrhea means an excessive fecal fat excretion of more than 7 g/d in the 72-hour fecal fat collection test [5,6].

Type 3c diabetes is a type of diabetes secondary to pancreatic diseases, which is also known as pancreatic diabetes and often occurs in CP patients.

Epidemiology and etiology

Globally, the incidence of CP is 9.62/100 000 person-years and the mortality rate is 0.09/100 000 person-years. Males have more than twice the incidence of CP than females [7]. The incidence of CP in American adults is 24.7/100 000 persons and the prevalence is 91.9/100 000 persons in 2014 [8]. In Japan, the incidence is 14.0/100 000 persons and the prevalence is 52.4/100 000 persons in 2011 [9]. The prevalence of CP in India is 125/100 000 persons, the highest in the world [10]. In China, the prevalence of CP in 2003 was about 13.5/100 000 persons and showed an increasing trend year by year [11].

The pathogenic factors of CP include genetic factors, environmental and/or other factors. Alcoholism is one of the main pathogenic factors in CP, accounting for 50%–60% of CP in Western

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countries and Japan [9,12] and about 20% of CP in China [13]. It is currently believed that genetic factors play a very important role in the pathogenesis of CP. Common susceptibility genes were found, notably *PRSS1, SPINK1, CTRC* and *CFTR* [14–16]. Hereditary CP is an autosomal dominant disease with a penetrance rate of 80%, which is often linked with the *PRSS1* gene. In China, the main pathogenic mutations of idiopathic CP is the c.194 + 2T>*C* in *SPINK1* gene [15]. In addition, other pathogenic factors of CP include hyperlipidemia, hypercalcemia, congenital abnormalities of the pancreatic duct, pancreatic trauma or surgery, and autoimmune diseases. Previous studies [17,18] have revealed that smoking is an independent risk factor for CP. Recurrent acute pancreatitis is also a high-risk factor for CP, with about one-third of recurrent acute pancreatitis patients eventually evolving into CP patients [3].

Diagnosis and staging

Symptoms

Abdominal pain, which is the most common clinical symptom of CP, characteristically occurs in the upper abdomen, often radiating to the back. Abdominal pain can be divided into two types: (i) type A is defined as intermittent abdominal pain, with no discomfort in the intermittent period; (ii) type B is a persistent abdominal pain, characterized as long-term, continuous pain or frequent aggravation of pain [19]. In China, type A accounts for the majority (more than 80%) of abdominal pain in CP patients while type B accounts for 5%, and about 10% of patients have no symptoms of abdominal pain [13].

For patients with pancreatic exocrine insufficiency, there may be no specific symptom in the early stage of the disease. With the progression of the disease, weight loss, malnutrition, and steatorrhea may occur. The incidence of steatorrhea in CP patients in China is 22.9% [20]. Pancreatic endocrine insufficiency manifests as impaired glucose tolerance or diabetes. The incidence of diabetes in patients with CP in China is 28.3% [21]. The complications of CP are pseudocysts, common bile duct stenosis, duodenal obstruction, pancreatic fistula, pancreatic portal hypertension, pancreatic ascites and pseudoaneurysm. After a diagnosis of CP, about 1.3% of patients progressed into pancreatic cancer during an 8-year follow-up [22].

Signs

The most common sign is upper abdominal tenderness. There may also be peritoneal irritation during acute attacks. Due to digestive malabsorption, patients may suffer weight loss and malnutrition, which may affect the development of adolescent patients. When a large pancreatic pseudocyst occurs, a mass can be felt in the abdomen. If the pancreatic head is significantly fibrotic or the lower part of the common bile duct is compressed by pseudocysts, jaundice may occur.

Imaging examinations

X-ray may reveal large radiopaque calculus in some CP patients.

Abdominal ultrasound usually reveals hyper-echoic lesions in the pancreas with acoustic shadow and changes of pancreatic duct morphology. With low diagnostic sensitivity, ultrasound is only used as a preliminary screening for CP. In addition, ultrasound may be helpful in detecting CP complications, such as pseudocysts.

The characteristics of computed tomography (CT) for CP include pancreatic calcification, pancreatic duct dilatation and pancreatic atrophy. The diagnostic sensitivity and specificity of a CT test are over 80% and 90%, respectively [23]. CT is the best modality to find pancreatic calcification, with the potential for detecting even micro-calcifications in the pancreas. The diagnostic value of conventional magnetic resonance imaging (MRI) scan for CP is similar to that of CT. MRI is sensitive to pancreatic parenchymal changes, but not as good as CT for detecting calcification and calculus. Magnetic resonance cholangiopancreatography is mainly used to examine lesions of the bile and pancreatic ducts, such as main pancreatic duct dilatation or stenosis.

The main features of CP under endoscopic ultrasonography (EUS) include abnormalities of pancreatic parenchymal and pancreatic duct, such as pancreatic duct stones, and pancreatic duct dilatation or stenosis. EUS has an advantage of high sensitivity in the diagnosis of early CP compared with other tests [24]. EUS-guided fine needle aspiration biopsy is mainly used for differential diagnosis between mass-type CP and pancreatic cancer [25].

Endoscopic retrograde cholangiopancreatography (ERCP) is an important method for the diagnosis of CP. However, because of its invasiveness, it is currently used only when it is difficult to make a diagnosis using other non-invasive tests or when treatment is required. According to the Cambridge classification [26], CP can be divided into three types under ERCP: (i) mild, with more than three abnormal branches of pancreatic duct while the main pancreatic duct is normal; (ii) moderate, with abnormal main pancreatic duct; (iii) severe, with obstruction of the main pancreatic duct, severe irregular dilatation and with stones or pseudocysts formation. Histology and cytology examinations during ERCP are valuable in distinguishing between malignant and benign lesions of the bile duct.

Laboratory tests

Pancreatic exocrine function test

This includes direct and indirect tests. The direct tests include secretin test, augmented secretin test, secretin-cholecystokinin test. They are considered the gold standard test for the evaluation of pancreatic exocrine function. However, it is used rarely in the clinical practice due to its high cost and invasiveness. The indirect test can be applied to testing stool, breath, urine or blood, with relatively low sensitivity and specificity. The two most common methods for testing pancreatic exocrine function are the fecal elastase-1 test and the ^{13}C mixed triacylglycerol breath test (^{13}C-MTG-BT). Secretin-stimulated magnetic resonance cholangiopancreatography can be used to evaluate pancreatic exocrine function, by semi-quantitatively assessing the increase in fluid in the duodenum.

Pancreatic endocrine function test

The diagnostic criterion of diabetes is mainly meeting the fasting blood glucose $\geq$ 7.0 mmol/L or random blood glucose $\geq$ 11.1 mmol/L or oral glucose tolerance test with 2-hour blood glucose $\geq$ 11.1 mmol/L [27]. CP patients without diabetes are advised to have a blood glucose test annually. Type 3c diabetes, also known as pancreatogenic diabetes, is characterized by negative results for pancreatic islet β-cell autoantibodies, decreased pancreatic polypeptide levels, and pancreatic exocrine insufficiency [28], which are often used to differentiate from other types of diabetes.

Genetic test

Genetic testing is highly recommended for CP patients who are diagnosed with idiopathic CP or adolescents (onset age younger than 20 years old) with CP or with a family history of pancreatic disease. The peripheral venous blood is withdrawn to test the *PRSS1, SPINK1, CTRC* and *CFTR* genes.

Other laboratory tests

Serum amylase is often abnormal when acute attacks happen or CP is complicated with pleural effusion or ascites. The serum calcium, lipids, parathyroid hormone, virus, and the immunoglobulin,

IgG4, help to identify the causes of CP. Patients with CP may also present with slightly elevated serum cancer antigen 19–9 (CA19-9). If CA19-9 is significantly elevated, pancreatic cancer should be considered. Other indicators, such as fat-soluble vitamins, serum albumin, prealbumin, magnesium, and retinol-binding proteins, help to evaluate the nutritional status of the patients.

Pathological examination

Pancreatic fine needle aspiration biopsy can be done under CT, abdominal ultrasound, or EUS guidance. Due to its invasive characteristics, biopsy, which is mainly used for the differential diagnosis of CP and pancreatic cancer, is not routinely performed in the clinical practice.

The decrease in pancreatic acinar cells and fibrosis are the basic histological changes observed in CP. Fibrosis includes two types, namely interlobular or perilobular fibrosis and intralobular fibrosis, which may be accompanied by chronic inflammatory cell infiltration of pancreatic tissue and pancreatic duct dilatation [29]. According to its pathological changes, CP can be classified into calcified, obstructive and inflammatory. Calcified CP is the most common type, with features of sporadic interstitial fibrosis, intraductal protein embolus, stones and pancreatic duct injury. Obstructive CP manifests as dilatation of the proximal pancreatic duct and acinar cell atrophy due to the obstruction caused by fibrous tissues. Inflammatory CP is characterized by pancreatic fibrosis, atrophy and monocyte infiltration. The pathological changes of extra-pancreatic organs include biliary obstruction, portal vein compression, splenic vein thrombosis, ascites and duodenal obstruction.

Diagnostic criteria

The diagnostic criteria of CP include two parts, major and minor criteria. According to the revised Japanese clinical diagnostic criteria for CP [30], the major diagnostic criteria are: (i) definite imaging findings, and (ii) definite pathological findings; the minor diagnostic criteria are: (i) repeated upper abdominal pain; (ii) abnormal blood amylase; (iii) pancreatic exocrine insufficiency; (iv) pancreatic endocrine insufficiency; (v) pathogenic mutations; and (vi) history of heavy drinking. The diagnosis of CP can be confirmed by one of the major diagnostic criteria; or at least two minor diagnostic criteria (Fig. 1).

Clinical staging

Clinical staging is useful for informing treatment choices according to the course and clinical manifestations of CP (Table 1). According to pancreatic functions, CP can also be classified into compensated stage and decompensated stage.

Treatment and prognosis

The main principles of treatment for CP are to eliminate the causative factors, relieve symptoms, improve pancreatic functions, decrease complications and improve the patient's quality of life.

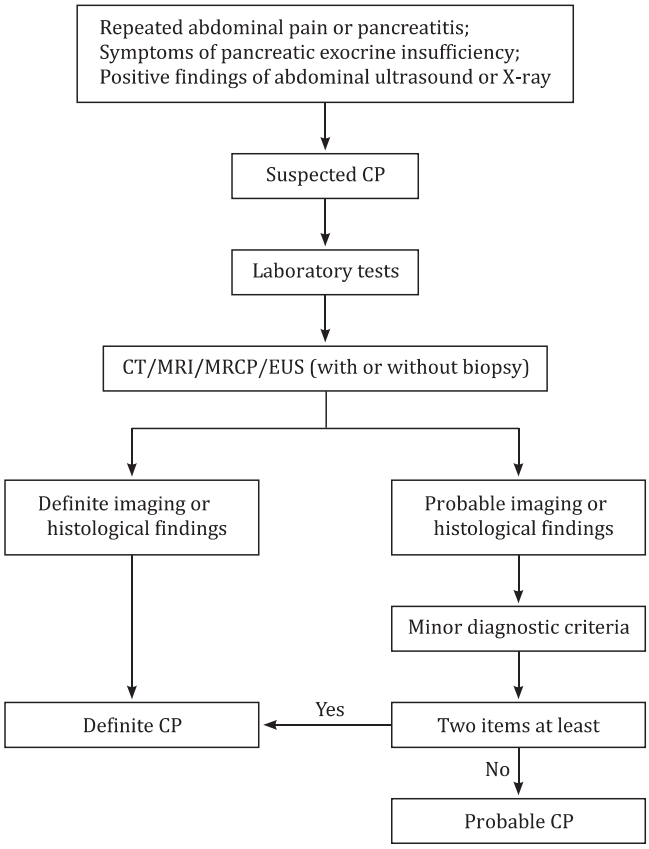

Fig. 1. The diagnosis flow chart of chronic pancreatitis.
CP: chronic pancreatitis; CT: computed tomography; MRI: magnetic resonance imaging; MRCP: magnetic resonance cholangiopancreatography; EUS: endoscopic ultrasonography.

Basic management

CP patients are supposed to abstain from alcohol and smoking, avoid an excessive high-fat and high-protein diet, and exercise properly.

Medical therapy

Treatment of pancreatic exocrine insufficiency

Oral pancreatic enzyme replacement therapy (PERT) is the first choice for treatment of pancreatic exocrine insufficiency. Clinically, an enteric-coated pancreatin, containing a highly active lipase, may be chosen. The addition of a proton pump inhibitor or a histamine type-2 receptor antagonist is helpful to improve fat digestion in patients with an unsatisfactory response to PERT. For patients with malnutrition, a proper diet plus PERT is recommended. Supplement of medium-chain triglycerides may be optional, if necessary. When fat-soluble vitamins are insufficient, vitamin D should be supplemented appropriately. There are no clinical, evidence-based recommendations regarding supplementing vitamins A, E, and K [31].

Table 1
Clinical stage of chronic pancreatitis.

Clinical stages	Manifestations
Stage 0 (subclinical)	Asymptomatic
Stage I	Abdominal pain or acute pancreatitis without pancreatic function insufficiency
Stage II	Pancreatic endocrine or exocrine insufficiency
Stage III	Pancreatic endocrine and exocrine insufficiency
Stage IV	Pancreatic endocrine and exocrine insufficiency without pain

Treatment of diabetes

In patients with diabetes, it is recommended changing the lifestyle with respect to diet and physical activities. For patients with suspected insulin resistance, metformin is the first choice if there is no contraindication. Other oral hypoglycemic drugs are not recommended because of significant adverse events. When oral drugs are ineffective, insulin treatment is the next step. In patients with severe malnutrition, insulin treatment is the first choice [31]. Additionally, hypoglycemia should be avoided because CP patients with diabetes are more sensitive to insulin.

Pain management

PERT, antioxidants and somatostatin may be effective for pain relief [32–34]. The standard guideline for analgesic therapy in CP should comply with the principles of the "pain relief ladder", provided by the World Health Organization (WHO). Oral drugs are the first choice. Step one, acetaminophen is the preferred analgesic, one of the non-steroidal anti-inflammatory drugs, with a lower incidence of adverse effects in the digestive tract. Step two, we should choose weak opioids, such as tramadol. Step three, analgesics should be the strong opioids selected for treatment. It has been estimated that up to 6% of patients with opioid therapy may develop "narcotic bowel syndrome", which is a paradoxical increase in abdominal pain when the opioid dose is increased, due to opioid-induced hyperalgesia of the somatic tissues [35].

Endoscopic treatment is effective in patients with an obstructive type of pancreatic pain caused by pancreatic duct stenosis or stones in the pancreatic duct. Other interventional methods, such as CT or EUS-guided coeliac plexus block, are not recommended as routine therapy, with short episodes of pain relief and a high incidence of adverse events [36]. Surgical treatment is optional when both medication and endoscopic therapy are ineffective. For CP patients with pain and main pancreatic duct dilatation, surgery is superior to endoscopic therapy in long-term pain relief [31].

Endoscopic therapy

The main indications for endoscopic treatments for CP include pancreatic duct stones, pancreatic duct stenosis, pancreatic pseudocysts and bile duct stricture. Endoscopic treatments are beneficial to relieve abdominal pain and improve a patient's quality of life.

Treatment of main pancreatic duct obstruction

CP can be divided into two types, according to whether the main pancreatic duct is obstructed or not. Obstruction of the main pancreatic duct is usually caused by pancreatic duct stenosis, pancreatic stones or abnormal pancreatic duct anatomy [13]. For patients with pain and main pancreatic duct obstruction, endoscopic treatment can relieve symptoms effectively. The complete and partial remission rate of pancreatic pain is 71% and 24%, respectively [37]. Endoscopic treatment is the preferred method for obstructive pain. The clinical response should be evaluated at 6–8 weeks. If it appears unsatisfactory, surgical treatment may be considered [31].

Treatment for stones in the pancreatic duct

Stones in the pancreatic duct can be divided into radiopaque and non-radiopaque. Stones may be single or multiple, mainly in the head of the pancreas [37]. For some small stones in the main pancreatic duct, ERCP can complete drainage successfully. For radiopaque stones larger than 5 mm in the main pancreatic duct, the best treatment choice is extracorporeal shock wave lithotripsy (ESWL) [38]. After the stones are fragmented successfully, ERCP may be the next step. The clearance rate with combined ESWL and ERCP treatment for stones in the main pancreatic duct is more than 70%, and the drainage rate is 90% [37,39]. Compared with combined ESWL and ERCP treatment, ESWL alone may also be effective for stone removal and pain relief [40]. The incidence rate of post-ESWL complications is about 6% and complications mainly include pancreatitis, hemorrhage, steinstrasse, perforation, and infection. Most complications can be cured with conservative treatment [41].

Treatment for main pancreatic duct stenosis

The principles of treatment are to relieve the stenosis and drain the pancreatic juice. Stent placement in the pancreatic duct during ERCP is the main treatment, supplemented by pancreatic duct sphincter incision, stenosis expansion and other operations. The pain remission rate is more than 70% [42]. Single plastic stenting is preferred, which can be exchanged either at regular intervals or "on-demand" in patients with a recurrence of pain and main pancreatic duct dilatation. The stent is usually left for 6 to 12 months [43]. If the stenosis persists after 12 months of 10-Fr single stent placement, multiple plastic stents or fully covered self-expandable metallic stents are recommended [44]. During ERCP, if intubations fail repeatedly because the main pancreatic duct is severely stenotic or distorted, the incision of duodenal minor papilla can be tried. For patients who have a failed ERCP, EUS-guided pancreatic duct drainage may be considered [45]. But this method is difficult and risky and therefore, it is only recommended in some experienced hospitals.

Treatment of common bile duct stricture secondary to CP

The incidence of CP complicated by benign common bile duct stricture is approximately 15%, with about half of cases symptomatic [13]. Symptoms, such as recurrent acute cholangitis, obstructive jaundice or persistent (over one month) cholestasis, are indications for stenting. Temporary biliary stenting, usually for one year with regular stent exchange in the case of plastic stents, is the mainstay of treatment. Multiple simultaneous plastic stents or covered self-expandable metallic stents are recommended with a long-term success rate of 90% [46,47], which is obviously higher than that with single plastic stents [48].

Treatment of pancreatic pseudocyst

Pancreatic pseudocysts that are symptomatic, combined with complications (infection, bleeding or rupture), or enlarging, are supposed to be treated [43]. The incidence of CP pseudocysts in China is about 18% and men have a higher risk than women [49]. For patients with symptomatic pancreatic pseudocysts, endoscopic treatment is preferred, with a success rate of 70%–90% [50,51], which is similar to surgery [52]. For small (<6 cm) pancreatic pseudocysts communicating with the main pancreatic duct in the head or body of the pancreas, transpapillary drainage is preferred. For non-communicating pancreatic pseudocysts, the EUS-guided transgastroduodenal mucosa drainage is an option.

Endoscopic treatment for pediatric CP

In teenager, CP usually presents as episodes of abdominal pain. Compared with adults, pediatric patients have a lower prevalence of complications, including diabetes, steatorrhea, and bile duct stricture [53]. Endoscopic treatment (ERCP, ESWL) can relieve abdominal pain effectively and reduce the incidence of pancreatitis with an effective rate of 50%–70% [53–55]. The main complication of endoscopic treatment is postoperative acute pancreatitis, which is similar to that of adults. Endoscopic treatment of adolescent CP is safe and effective.

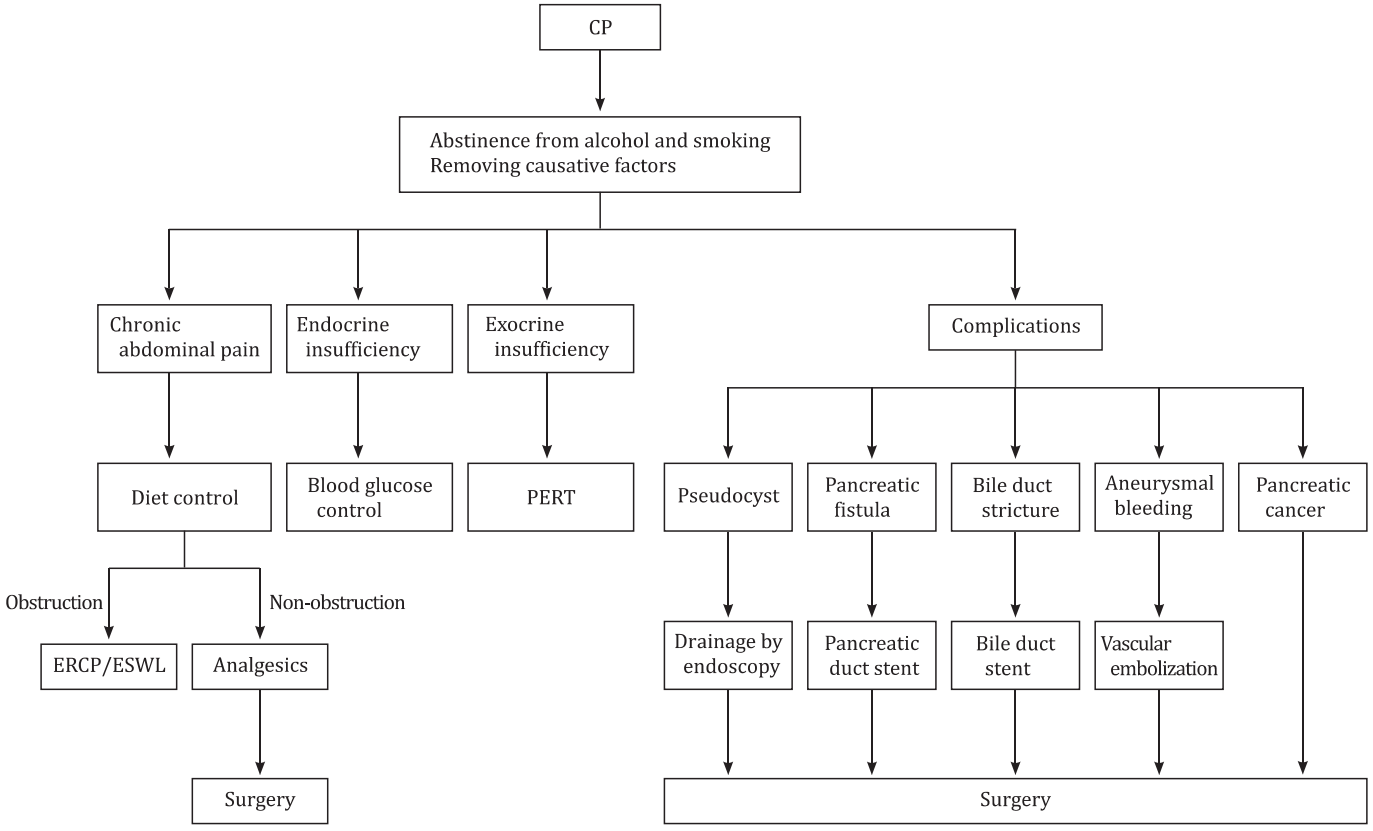

Fig. 2. The treatment flow chart of chronic pancreatitis.
CP: chronic pancreatitis; ERCP: endoscopic retrograde cholangiopancreatography; ESWL: extracorporeal shock wave lithotripsy; PERT: pancreatic enzyme replacement therapy.

Surgical therapy

Indications

Patients should consider surgical therapy under the following conditions: (i) intractable pain that cannot be alleviated by conservative treatment or endoscopic treatment; (ii) complicated by biliary obstruction, duodenal obstruction, pancreatic pseudocyst, pancreatic portal hypertension with hemorrhage, pancreatic fistula, pancreatic ascites, or pseudoaneurysm, and not suitable or ineffective for medical and interventional treatment; (iii) suspected malignancy; and (iv) failed endoscopic treatment.

Surgical methods

Etiology, characteristics of lesions, operators' experience, complications and other factors are considered when selecting surgical options, which mainly include pancreatectomy, pancreatic duct drainage and combined operation.

Standard pancreaticoduodenectomy or pylorus-preserving pancreaticoduodenectomy are indicated for situations when there is an inflammatory mass at the head of the pancreas complicated by pancreaticobiliary and duodenal obstruction, malignancy cannot be ruled out, or there are multiple stones in the pancreatic duct branches in the head of the pancreas. A pancreatic body and tail resection is suitable for patients who have inflammatory lesions, main pancreatic duct stenosis or stones concentrated at the tail of the pancreas. A mid-pancreatic resection is applied to the inflammatory mass localized at the pancreatic neck while the pancreatic head is basically normal and the lesion at the tail of pancreas is obstructed caused by the inflammatory lesion of the pancreatic body. Total pancreatectomy should be considered in patients with no duct system dilatation, when there are multiple stones in the pancreatic duct branches, when there is refractory pain caused by previous surgical treatment, or there are total-pancreatic inflammatory changes. Additionally, islet autotransplantation combined with total pancreatectomy is recommended for preserving the patient's endocrine function.

Decompression of pancreatic duct maximally preserves pancreatic functions. Lateral pancreaticojejunostomy is the main surgical technique suitable for patients who have stones at the main pancreatic duct with a dilated main pancreatic duct and no inflammatory mass.

Mixed techniques preserve the integrity of the duodenum and biliary tract while resecting lesions of the pancreatic head, relieving obstruction of the pancreatic and bile ducts and with pancreatic duct drainage. The main surgical methods include Beger's and modified Beger's, Frey's, Izbicki's (modified Frey's) and Berne's procedures. Beger's procedure, which is also known as the duodenum-preserving pancreatic head resection, is mainly used for CP patients with an enlarged pancreatic head. Compared with pancreaticoduodenectomy or pylorus-preserving pancreaticoduodenectomy, the incidence of postoperative complications and the improvement of life quality are similar [56]. Frey's procedure is indicated for patients with a small mass at the pancreatic head accompanied by pancreatic duct dilatation and stones at the body and tail of the pancreas. The range of resection of the pancreatic head in this operation is smaller than the former, but there is a probability for local recurrence and insufficient drainage. Compared with Frey's procedure, Izbicki's procedure has a larger range of pancreatic head resection, which includes the central part of the pancreatic uncinate and part of the ventral pancreatic tissue along the long axis of the pancreatic duct, as a "V" shape. The procedure achieves drainage of both the main and the accessory pancreatic ducts and has a better effect. Berne's procedure resects part of the pancreatic head to improve drainage of both the bile and

pancreatic duct while preserving the dorsal pancreatic tissue. The procedure is simpler and combined with fewer serious complications and shorter hospital stays. It is similar to Beger's procedure for pain relief and reserves pancreatic endocrine and exocrine functions [57].

Treatment process of CP

The treatment of CP is comprehensive and multidisciplinary, including internal medicine, digestive endoscopy, surgery, radiology, anesthesia and nutrition. The treatment flowchart is shown in Fig. 2. A MEES (Medicine-ESWL-Endotherapy-Surgery) step-by-step mode is recommended.

Prognosis and follow-up

CP is a progressive disease that some patients with persistent progression may develop endocrine and/or exocrine insufficiency and even pancreatic cancer. Patients are supposed to be followed up regularly with an evaluation of their endocrine and exocrine functions, nutritional status and quality of life by laboratory tests, CT/MRI examinations, and questionnaires. In addition, for mass-type CP patients, follow-up is recommended every three months, given its significant association with pancreatic cancer, which may be diagnosed through tumor markers, imaging and some other examinations. If there are no obvious abnormalities, the follow-up period can be prolonged appropriately.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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