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# Chronic Pancreatitis With or Without Acute Exacerbations: Novel Options for Pain Control

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## Introduction

Chronic pancreatitis (CP) is a benign inflammatory disease of the pancreas. The mechanism of pain is incompletely understood although the knowledge of this disease starts with the study of Sarles et al. in 1965 [5]. Irreversible morphological changes take place with progressive loss of the exocrine and later endocrine function of the gland due to fibrosis [1].

Pancreatitis: inflammation of the pancreas is subdivided clinically in its chronic and acute form.

This subdivision between acute and chronic pancreatitis into completely different entities must be revised. It is rather a continuum of disease where patients may show an evolution from acute to chronic pancreatitis. Both stages were described as being at separate ends of the same spectrum [2].

Acute pancreatitis, mainly characterized by acute pain due to inflammation and tissue necrosis is a transient event. During the recovery period, the gland is more vulnerable to alcohol, metabolic and oxidative stress, and cytokines. The latter are up regulated during the acute inflammation. Chronic pancreatitis is the ongoing process which consists of permanent and irreversible damage [3]. Estimates of annual incidence of chronic pancreatitis provide ranges from 5 to 12 cases per 100,000 persons. Furthermore depending on the population being studied, wide variations in incidence and prevalence figures are found [4].

Chronic pancreatitis is considered a common disease state, but it has different causes, 51 % is attributed to alcohol abuse. There are also autoimmune, hereditary (like in cystic fibrosis), metabolic (hypercalcemia, hyperlipidemia), tropical, and idiopathic forms of pancreatitis. Idiopathic chronic pancreatitis reflects that no cause can be identified. Chronic renal failure and hypercalcemia are described as risk factors.

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According to the etiology, the different forms of pancreatitis have a difference in age of onset, sexual differentiation, and life expectancy. Hereditary pancreatitis starts between 10 and 14 years, whereas alcoholic pancreatitis starts around 40 years of age [5].

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## Predisposing Factors

Major predisposing risk factors for chronic pancreatitis may be categorized as either (1) toxic-metabolic, (2) idiopathic, (3) genetic, (4) autoimmune, (5) recurrent and severe acute pancreatitis, or (6) obstructive (TIGAR-O system). After classification, staging of pancreatic function, injury, and fibrosis becomes the next major concern.

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## Etiology

The different possible etiologies for chronic pancreatitis are listed in Table 9.1

Increased daily alcohol intake has been linked to a higher risk for chronic pancreatitis. There is, however, no known threshold value below which the disease does not occur [6, 7].

Although it is difficult to determine with certainty the involvement of alcohol intake in the pathogenesis of pancreatitis, in almost all patients at least 5 years (and sometimes 10 years) of excessive intake preceded the development of chronic pancreatitis [4]. A strong association of simultaneous alcohol intake and smoking has been demonstrated to increase the risk for chronic pancreatitis.

For *alcoholic pancreatitis* the age of onset is between 40 and 50 [5]. There is mortality within 10 years after the diagnosis of 30 %. After a period of acute inflammation, stellate cells in the pancreas get activated due to cytokines as a product of the inflammation but also by ethanol and its metabolites. Secondary this induces the increased fibrosis of the pancreas [7–9].

**Table 9.1** Possible etiologies of chronic pancreatitis

Alcoholic pancreatitis
Hereditary pancreatitis
Autoimmune pancreatitis
Metabolic pancreatitis (hypercalcemia, hyperlipidemia)
Tropical pancreatitis
Idiopathic

One could presume that death is caused by multiple organ failure, sepsis, surgical complications or late complications of diabetes mellitus. But, the most prominent cause of death is the patients' lifestyle and alcohol related accidents. There is also an increased risk of lung cancer, esophageal cancer, and pancreatic cancer. These patients also seem to have an increased risk for cardiovascular disease.

*Tropical pancreatitis*, as the name suggests, is predominantly found in tropic regions such as Southwest India, Africa, Southeast Asia, and Brazil. Initially it was judged that tropical pancreatitis was restricted to areas within 30° latitude from the equator. The mean age of onset is 24 years. In endemic areas the prevalence may be as high as 1 in 500 persons. The pathophysiology is unclear, genetic mutations, environmental triggers, viral and parasitic infections have been suggested.

Clinical manifestations of tropical pancreatitis are: abdominal pain, severe malnutrition, and exocrine or endocrine insufficiency. Endocrine insufficiency seems to be directly related to diabetes. Steatorrhea is rare because of the very low-fat diet. In more than 90 % of the cases pancreatic calculi are present [4].

In families with *hereditary pancreatitis*, mutations in PRSS1 [protease, serine, 1 (trypsin 1) belong to a family of genes called serine peptidases] may cause chronic pancreatitis. Other mutations are considered cofactors to the development of chronic pancreatitis by increasing the susceptibility, or as modifier genes that increase the pace or severity of the disease. Several studies suggested that less severe CFTR (cystic fibrosis transmembrane conductance regulator) gene mutations and SPINK1 (Pancreatic secretory trypsin inhibitor (PSTI) also known as serine protease inhibitor Kazal Type 1) mutations may be associated with idiopathic chronic pancreatitis.

There are three major genetic factors that may play a role in chronic pancreatitis.

## PRSS1

In normal conditions, trypsinogen is converted to the active trypsin. Three versions of trypsinogen can be identified: cationic, anionic, and mesotrypsinogen with respectively the involvement of PRSS1 gene, PRSS2 gene, and PRSS3 gene.

In 1996 Whitcomb et al. [10] isolated the first responsible mutation in the cationic trypsinogen gene (*PRSS1*). In the mutated families, there is an enhanced intra-pancreatic trypsinogen auto activation with secondary initiation of chronic pancreatitis. On the other hand, mutations of the chromosome PRSS2 have a disease protective effect for chronic pancreatitis.

## SPINK 1

Serine protease inhibitor Kazal Type 1 or pancreatic trypsin inhibitor is an important inhibitor of the intra-pancreatic conversion of trypsinogen to trypsin. Mutation in the gene reduces the inhibition of auto activation with sequential activation of the zymogenes and auto digestion.

## CFTR

Cystic fibrosis transmembrane conductance regulator (CFTR) regulates ductal bicarbonate secretion in the pancreas. Mutations of the CFTR gene are associated with cystic fibrosis, an autosomal recessive disease, with pulmonary and pancreatic dysfunction.

*Autoimmune pancreatitis* refers to a distinct chronic inflammatory and sclerosing disease of the pancreas. It is accompanied by dense infiltration of the pancreas, and sometimes other organs with lymphocytes and plasma cells that express IgG4 on the surface. *H. pylori* infection can play a potential role in autoimmune pancreatitis. Because of the frequent presence of extra pancreatic manifestations such as biliary strictures, hilar lymphadenopathy, sclerosing sialadenitis, retroperitoneal fibrosis, and tubulointerstitial nephritis, it is assumed that autoimmune pancreatitis may be one manifestation of what has been called IgG4-related sclerosing disease or IgG4-related systemic disease.

The disease occurs most often after the age of 50 years and touches twice as much men than women. Clinically it presents as painless obstructive jaundice due to obstruction of the intra-pancreatic bile duct. It responds rapidly to glucocorticoid therapy. Most reports on autoimmune pancreatitis come from Japan and Asia. The overall prevalence is estimated to be 0.82.

## Obstructive Chronic Pancreatitis

Obstruction of the main pancreatic ducts may be caused by different factors such as tumors, scars, ductal stones, duodenal wall cysts, or stenosis of the papilla of Vater or the minor papilla. Obstructive chronic pancreatitis is, however, a distinct entity produced by a single dominant narrowing or stricture of the main pancreatic duct.

## Clinical Presentation

### Pain

Pain and more specifically abdominal pain is the most predominant symptom that is responsible for the decreased quality of life, a reduced appetite and consequently reduced food intake and malnutrition leading to dramatic weight loss. Chronic severe pain is often responsible for the progressive social isolation of the patients. The addictive behavior and the difficulty to control chronic pancreatic pain may lead to addiction for narcotic analgesics.

There are no firm pain patterns. Patients report mostly epigastric pain that may radiate into the back. Pain often increases after ingestion of high fat food. It is described as boring, deep, and penetrating. It is often associated with nausea and vomiting. Bending forward and assuming the knee-chest position on one side or clasping the knees to the chest may alleviate the pain. No clear evolution pattern of the pain can be found.

### Steatorrhea

When pancreatic lipase secretion is reduced to less than 10 % of the maximum output *steatorrhea* will occur. This is a feature of far-advanced chronic pancreatitis in which most of the acinar cells have been injured or destroyed. Maldigestion of fat, protein, and carbohydrates occur, but the maldigestion of fat occurs earlier and is more severe than protein or carbohydrate maldigestion. The median time to development of exocrine insufficiency has been reported as low as 5.6 years, but most studies report 13.1 years in patients with alcoholic chronic pancreatitis; 16.9 years in patients with late-onset idiopathic chronic pancreatitis, and 26.3 years in patients with early-onset idiopathic chronic pancreatitis. Significant weight loss due to maldigestion is uncommon. This is most commonly seen during painful flare ups, when pain, nausea, and vomiting prevent accurate food intake. In patients with chronic pancreatitis and steatorrhea deficiencies in fat soluble vitamins and specifically vitamin D may be observed.

### Diabetes Mellitus

Endocrine insufficiency is also a consequence of longstanding chronic pancreatitis and results in diabetes mellitus in approximately 80 % of the patients with chronic pancreatitis. This diabetes is classified as type 3.

## Less Common Symptoms

Jaundice  
Skin nodules  
Painful joints  
Abdominal distension  
Shortness of breath  
Pleural effusions and ascites

## Diagnostic Process

### Physical Examination

Physical examination does not give much additional information that allows fine tuning the diagnosis of chronic pancreatitis. Aside from the abdominal tenderness a palpable pseudocyst may occasionally be found and jaundice may be seen in presence of coexisting alcoholic liver disease or bile duct compression within the head of the pancreas.

## Diagnostic Tests

### Laboratory

#### Serum Test

In contrast with acute pancreatic disease, where serum lipases and amylase are elevated, these tests stay normal in chronic pancreatitis, and thus have no diagnostic value.

Complete blood count, electrolytes, and liver function tests are normal. Elevated serum bilirubin and alkaline phosphates can be indicative for compression of the intra-pancreatic part of the bile duct or pancreatic cancer.

In cases of autoimmune chronic pancreatitis, an elevated ESR, IgG4, rheumatoid factor, ANA, and anti-smooth muscle antibody titer can be detected.

Deficiencies of maldigestion of fat and proteins or vitamins like vitamin A, B12, and D can only be seen if 90 % of the glandular function is lost [11].

### Pancreatic Functional Testing

#### Exocrine Function

The pancreas secretes daily 1.5 L of fluid rich in pancreatic enzymes for the digestion of fats, starch, and proteins. Secretin and cholecystokinin (CCK) play a key role in the regulation by a hormonal and neuronal feedback mechanism. Testing the functional activity of the pancreas can be done directly or indirectly. In advanced chronic pancreatitis these tests are unnecessary as imaging tests reveal structural changes. On the contrary, these tests can be helpful to

diagnose the disease in an early stage. They can also be used as a guidance for adapting enzyme therapy.

*For direct testing*, the pancreas is stimulated by administration of a meal (Lundh test) or hormonal secretion stimulating products (CCK or secretin). Secretin stimulates the duct cells while CCK stimulates the acinar cells. Pancreatic fluid is collected by means of double lumen gastrointestinal tubes. Duodenal fluids are collected over 90 min. The fluids are analyzed to quantify enzymes (trypsin, amylase, lipase) and bicarbonate. The value of the bicarbonate and enzymes is a parameter to quantify the functional mass of pancreatic tissue. This test can reveal early stage chronic pancreatitis before the development of steatorrhea [12].

Endoscopic secretin test is now the reference test. Comparison of Pancreatic Functional Testing (PFT) with histological changes showed 67 % sensitivity and 90 % specificity of the secretin CCK test for chronic pancreatitis [13].

*Indirect tests* measuring the consequence of pancreatic insufficiency are more widely available. These tests are less sensitive and less specific in the diagnosis of chronic pancreatitis.

*Serum trypsinogen*: a low level trypsinogen has a high specificity for chronic pancreatitis. In case of normal level but with a clinical presentation of chronic pancreatitis the test should be repeated [14].

### Fecal Tests

Fecal fat is tested in a stool sample. Steatorrhea is suggestive for a loss of more than 90 % of the normal pancreatic exocrine enzyme secretory output. Fat malabsorption may also occur in cases of disease of the small intestinal mucosa.

### Fecal Chymotrypsin, Fecal Elastase 1

These tests show a poor sensitivity in early chronic pancreatitis and false positive testing in gastro intestinal disease.

### Endocrine Function

Serum glucose HBA1 determination can be used to assess the endocrine function. This is often sooner affected than the exocrine function.

### Genetic Analysis

Five pancreatitis susceptibility genes are established: cystic fibrosis transmembrane conductance regular gene (CFTR), pancreas secretory trypsin inhibitor gene (SPINK-1), chymotrypsinogen C gene (CTRC), calcium sensing receptor gene (CASR), and cationic trypsinogen gene (PRSS), linked to hereditary pancreatitis.

Routine full genetic analyses are not recommended since they are not necessarily for the diagnosis of chronic pancreatitis, they are expensive and generally do not alter management. On indication CFTR and SPINK are mostly performed.

## Imaging Studies

### Plain Film of the Abdomen

Plain X-rays of the abdomen can show diffuse calcifications this is pathognomonic in chronic pancreatitis but, it occurs late. Calcification primarily represents intraductal calculi, either in the main pancreatic duct or in the smaller pancreatic ductal radicles. Clinical relevance is very low.

### Ultrasound

Trans-abdominal ultrasound is a highly specific, inexpensive, and noninvasive screening test. In patients with thin bodies, trans-abdominal ultrasound can show the anatomy of the pancreas, parenchymal changes (atrophic and fibrosis), and ductal features suggestive of chronic pancreatitis (sensitivity, 60–70 %; specificity, 80–90 %).

Ultrasound also helps in ruling out other causes of epigastric pain, such as gallstones and aneurysmata. Complications of chronic pancreatitis, such as arterial pseudoaneurysms, left-sided portal hypertension (i.e., splenic venous thrombosis), and pleural effusions are readily detected with ultrasound. The pancreas is not always visualized if there is gas or in obese patients. Differential diagnosis between inflammatory processes and carcinomas are difficult [15].

### Endoscopic Ultrasonography

Endoscopic ultrasonography (EUS) is more sensitive in showing changes of the hyper echoic foci, hyperechoic strands, lobularity, hyperechoic duct, irregular duct, visible side-branches, ductal dilation, calcification, and cysts. The diagnosis of chronic pancreatitis can be made at an earlier stage of the disease, if more than two criteria for pancreatitis are in place [16].

Findings of pancreatic function tests, which can be considered standard for detecting early changes of chronic pancreatitis, have been compared with those of endoscopic ultrasound. Overall, endoscopic ultrasound and pancreatic function tests agreed in approximately 75 % of cases [17].

The feasibility of performing both endoscopic ultrasound and endoscopic pancreatic function tests during the same endoscopic session as a simultaneous assessment of pancreatic structure and function was demonstrated [17].

### Computed Tomography with Contrast

Computed tomography (CT) with contrast gives adequate information about pancreatic volume, calcifications, duct dilation when performed using thin slices through the pancreas, it is a reliable test for the diagnosis of advanced chronic pancreatitis.

CT has a sensitivity rate for advanced chronic pancreatitis of 74–90 % and a specificity of 84–100 %.

CT also allows the detection of complications, including pseudocysts, splenic artery pseudoaneurysm, and biliary duct involvement, pancreatic cancer or inflammatory masses and surrounding anatomical involvement [18].

Currently, CT is regarded as the imaging modality of choice for the initial evaluation of suggested chronic pancreatitis.

### **Magnetic Resonance Imaging, Magnetic Resonance Cholangiopancreatography**

Magnetic resonance imaging (MRI) has no radiation risk. It can demonstrate calcifications, atrophy, ductal abnormalities, and fluid filled cysts in T2 weighted images and may offer improved differentiation of neoplastic and inflammatory masses.

Contrast-enhanced MRI weighted images may offer improved differentiation of neoplastic and inflammatory masses.

Magnetic resonance cholangiopancreatography (MRCP) allows a noninvasive alternative to Endoscopic retrograde cholangiopancreatography (ERCP) for imaging the pancreatic duct.

When no abnormalities can be shown in physiologic conditions, and there is a clinical presentation indicative for chronic pancreatitis, secretin-enhanced MRCP might improve the detection of diseased pancreatic ducts. It also provides additional functional information regarding pancreatic exocrine function. As experience grows, MRI imaging, particularly MRCP, may be increasingly used for assessment and screening for chronic pancreatitis.

### **Endoscopic Retrograde Cholangiopancreatography**

Endoscopic retrograde cholangiopancreatography (ERCP) plays a role in gallstone pancreatitis and complicated acute and chronic pancreatitis. It is a highly sensitive radiographic test for chronic pancreatitis (sensitivity, 71–93 %; specificity, 89–100 %). As with most diagnostic tests, studies comparing ERCP with histology, the true gold standard, are lacking.

ERCP is not only a diagnostic tool but can also be used for therapeutic purposes. Pancreatic duct leaks or strictures can be stented as a bridge to surgery, common bile duct stones can be removed, pseudopancreatic cysts can be treated by stents, papillotomy for drainage or cystogastro of duodenostomy can be performed.

Pancreatic cancer diagnosis is possible but the accuracy of this technique is lower than with endoscopic ultrasonography.

ERCP carries a 5–10 % risk of inducing acute pancreatitis. Other less common risks include bleeding, infection, and perforation. In recent years, the role of ERCP in the diagnosis of pancreatic disease has decreased because safer and less invasive techniques have been developed [19].

### **PET Scan**

Patients with chronic pancreatitis are at risk of developing pancreatic cancer. Fluoro deoxy glucose positron emission tomography (FDG-PET) has a potential role as a diagnostic tool for detecting pancreatic cancer in long-standing chronic pancreatitis.

However in the specific case of autoimmune-related pancreatitis, an intense uptake is observed, which disappears after steroid therapy. This fact should be kept in mind because it may lead to falsely making a diagnosis of a neoplastic process [20–22].

### **Pain Evaluation/Testing**

Differential epidural anesthesia (DEA) is a test used for initial evaluation of the neural mechanism of the pain problem. In patients with visceral pain, DEA is used as a diagnostic modality to identify which patients should get celiac, splanchnic, or hypogastric blocks. It is not as precise as sometimes claimed [23, 24].

### **Pathophysiology of Pain Induced by Chronic Pancreatitis**

The study of the pain mechanisms has been complicated by the difficulties in producing animal models that mimic chronic pancreatitis [25].

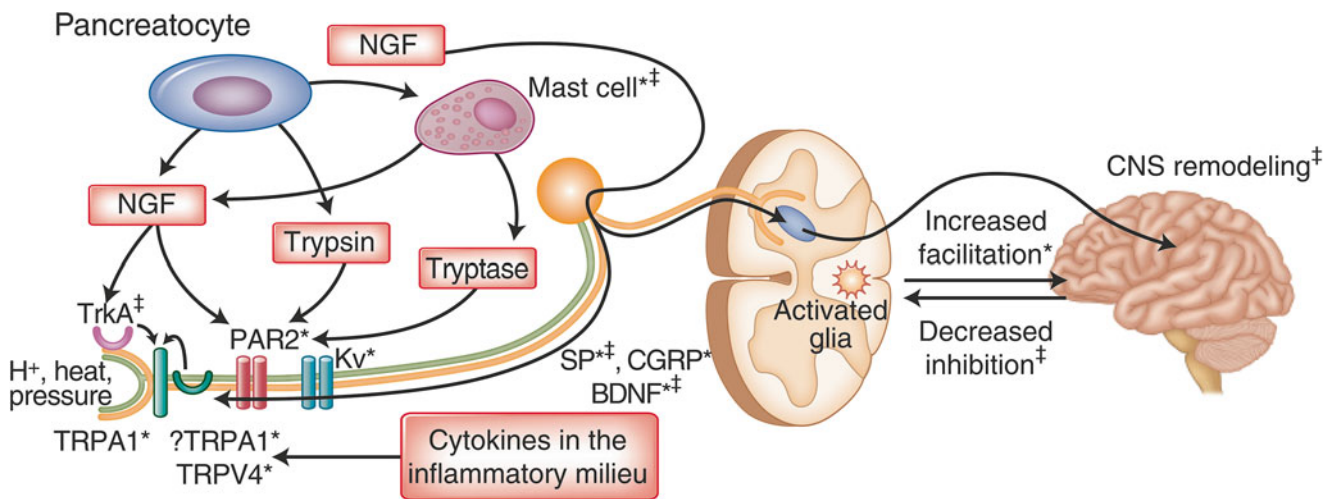
Pain in pancreatitis may be caused by different mechanisms. Over the years the theories shifted from mechanical to neurobiological pathogenesis. Pain can be divided into: [26].

1. Nociceptive pain
2. Neuropathic pain
3. Neurogenic inflammation

Nociceptive pain occurs after the activation of primary afferent neurons that respond to chemical or mechanical stimuli. The pain is proportional to the degree of stimulation. Chronic pancreatitis involves inflammatory infiltration of sensory nerves. In human and animal models with chronic pancreatitis, perineural infiltrates are found with a high percentage of eosinophils in which the degree of infiltrative disorder correlates with the severity of the pain [27]. In the presence of inflammation, ischemia, increased pressure and release of, for instance, bradykinins, prostaglandins, and substance P, nociceptors are activated, generating action potentials, and nociceptive pain thus develops [27].

One theory argues that increased pressure in the pancreatic duct leads to pain due to obstruction. Obstruction of the pancreatic duct can cause an “overpressure” proximally. This explanation of the pain is the basis for endoscopic and surgical drainage procedures.

Subsequently, several studies into overpressure in the pancreatic duct were carried out (preoperatively and during endoscopic retrograde cholangio pancreatography with manometry of the pancreatic duct), which showed inconsistent results. There are three studies in which the pressure in the pancreatic parenchyma was determined before surgery or partial pancreatic resection. Although higher pressures were found in the patients’ parenchyma and the pressures were lower



**Fig. 9.1** Peripheral mechanisms of pain in chronic pancreatitis. A conceptual paradigm for the pathogenesis of pain in pancreatitis. Biological factors such as NGF that are produced in chronic pancreatitis can sensitize the nociceptor neuron by upregulating several key molecules, such as the receptor TRPV1 and neurotransmitters such as SP and CGRP, as well as by downregulating potassium channels. NGF is produced by pancreatic cells as well as mast cells. Mast cells also produce trypsin that along with trypsin can activate the PAR2 receptor, which is also expressed by nociceptors. In addition to TRPV1, several other receptors, such as TRPA1 and TRPV4 are capable of inducing noxious thermal,

chemical, or mechanical stimuli. The inflammatory milieu in chronic pancreatitis also contains many different kinds of cytokines and other inflammatory mediators that act on the neurons and further sensitize and/or activate them. Superscripts denote whether these factors have been implicated in the pathogenesis of pain in animal (*asterisk*) or human studies (*double dagger*). *BDNF* brain-derived neurotrophic factor, *CGRP* calcitonin gene-related peptide, *Kv* voltage activated potassium channels, *NGF* nerve growth factor, *PAR2* protease activated receptor 2, *SP*, substance P, *TrkA* tryptomyosin-related kinase A receptor, *TRPV2* vanilloid receptor

after the procedure, there was no consistent correlation with the pain [28].

Other factors that may cause nociceptive pain in chronic pancreatitis include: obstruction of the duodenum or common bile duct (ductus choledochus), infiltration of the retroperitoneum, pseudocyst formation with compression of the surrounding organs, obstruction of the ductus pancreaticus due to fibrosis/stones/protein plugs, pancreatic ischemia due to atherosclerosis, gastric or duodenal ulcers, and meteorism due to malabsorption [29].

Neuropathic pain involves a change of the sensory nerves or the central nervous system itself. This change or damage is caused by (but is not dependent on for perpetuation) nociceptive activation. It has been shown that changes occur in the neurons innervating the pancreas that are located in the spinal ganglia (dorsal root ganglia) [29]. Patients with chronic pancreatitis appear to show generalized hyperalgesia, possibly based on deep sensitization [29]. Neurogenic inflammation is another proposed mechanism for pain. Cell death and tissue inflammation cause changes in the pH and the release of ions and inflammatory products such as cytokines and ATP. These inflammatory substances have direct as well as indirect effects on the nerve fibers and their ganglia once neuropathic pain develops. Neurogenic inflammation itself induces the production and increased release of neuropeptides, which then reinforces the inflammatory reaction in the tissues [30].

Since 2005, however, a rodent model for chronic pancreatitis with face and predictive validity was published. Studies with this model allowed to identify mechanisms of pancreatic pain. Its signals are transmitted via primary afferent nociceptors and induced by inflammation, morphological changes in peripheral nerves, and damage to the tissue. A cascade of events is initiated that includes central and peripheral sensitization and upregulation of various molecules. The group of Pasca di Magliano [25] formulated a paradigm with regard to the pain mechanisms of chronic pancreatitis (Fig. 9.1).

## Treatment Options

The treatment of chronic pancreatitis should ideally be disease oriented, however, because pain is often the first sign that stimulates the patient to search medical help, and the disease has already reached a stage where it is irreversible, the management will be predominantly palliative. We focus here on the pain management of chronic pancreatitis.

## Lifestyle Adjustments

Because chronic pancreatitis is in the majority of the cases due to alcohol abuse, the first treatment step is complete abstinence of alcohol, even in those forms of pancreatitis that

are not linked with alcohol consumption. Smoking cessation is highly recommended. These changes in lifestyle reduce pain and improve life expectancy [31–33].

## Pharmacological Pain Management

Pharmacological management of pain induced by chronic pancreatitis follows the guidelines of the three step WHO pain ladder for the management of cancer pain [34]. It must be stressed that, particularly the patients who suffer pain from alcoholic chronic pancreatitis, there is a propensity toward addiction. Moreover these patients have frequently liver and renal insufficiency, factors that must always be considered when establishing the treatment schedule.

### Peripheral Analgesics

For the management of mild to moderate pain, paracetamol (acetaminophen) is the medication of first choice. It has good analgesic and antipyretic properties and few side effects, especially no gastrointestinal side effects in the recommended dosage.

### Nonsteroidal Anti-Inflammatory Drugs

The inflammatory component of pain may justify the use of nonsteroidal anti-inflammatory drugs (NSAIDs) that exert an inhibitory activity on COX-1 and COX-2 to varying degrees. Attention should be paid to the potential side effects that vary from dyspepsia and skin disorders to gastric ulcerations and renal toxicity.

Overexpression of COX-2 in chronic pancreatitis has been shown [35]. The use of selective COX-2 inhibitors may be considered, however, the contribution of COX-1 inhibitors should not be underestimated in the treatment of pronociceptive factors such as prostaglandins as part of the treatment of chronic pancreatitis. Moreover, long-term use of selective COX-2 inhibitors presumably increases the risk of cardiac disease, which makes these drugs less suitable for the treatment of chronic pancreatitis. There are even case reports that suggest COX-2 inhibitors induce flares of acute pancreatitis.

### Opioids

The second and third step in the WHO pain ladder consists in the use of opioids of varying strength. In-line with the WHO recommendations a treatment around the clock with long acting preparations is recommended. To obtain stable plasma levels and hence pain control, but also to limit the risk of addiction. Fast acting opioid preparations may be used for the management of breakthrough pain. Common side effects such as nausea and vomiting usually disappear when the treatment is continued. At the start of treatment those side effects can be managed with low doses of a centrally acting

antiemetic or haloperidol. Constipation, a common side effect of opioid treatment is preferentially managed with laxatives started together with the opioid therapy.

Opioids act by binding to one of the opioid receptor ( $\mu$ ,  $\kappa$ , and  $\delta$ ). These receptors are found on the neuronal cell membranes, but also in other organs, such as the  $\mu$  receptors in the gut and the  $\mu$ ,  $\kappa$ , and  $\delta$  receptors in the sphincter of Oddi. This is a muscular valve in the duodenal wall that controls the release of bile and pancreatic juice, which is influenced by the hormone CCK. There is a tonic rest pressure as well as phasic antegrade contractions in this sphincter. Opioids result in an increase of the contraction frequency, amplitude, and rest pressure. As this effect can only partly be counteracted by naloxone (an opioid-antagonist), it is likely that the effect of morphine on the sphincter of Oddi is mediated by several opioid receptors. The degree to which various morphinomimetics influence the pressure in the sphincter of Oddi has been studied. The results vary, partly also because different manometric techniques were used. From the different studies, it can be concluded that all opioids cause an increase of the sphincter pressure. However, there are no studies that justify the conclusion that increased pressure of the sphincter of Oddi has an effect on the development or deterioration of acute or chronic pancreatitis [36–39].

### Co-analgesics

The co-analgesics, act predominantly on neuropathic pain but are also used for the treatment of chronic pancreatitis. Tricyclic antidepressants, SSRI and SNRI act on the peripheral of a central nerve stimulation. Calcium channel blockers like pregabalin, gabapentin are strongly recommended in chronic pancreatitis. Olesen's group demonstrated in a randomized controlled trial that pregabalin reduces pain in chronic pancreatitis [40–43].

Additionally the tricyclic antidepressants act on the depressive symptoms that are frequently seen in chronic pain patients.

### Ketamine

Ketamine has been used in many chronic pain states and also in cancer pain [44]. S-ketamine infusion in chronic pancreatitis pain patients reduces hyperalgesia immediately after infusion. It might have a role in those patients who have exhausted the full range of medical and surgical options [44, 45].

### Non-analgesics

#### Pancreatic Enzyme Supplements

The rationale behind the use of pancreatic enzymes is found in the fact that they degrade the CCK releasing factor, thus lowering the CCK levels. Through this mechanism pain is reduced. It is important to note that only enteric coated

formulations, that allow liberation of the enzymes in the duodenum, have a positive effect on pain. The best results of pancreatic enzyme supplementation are noted in small duct disease or minimal change chronic pancreatitis [28].

### Octreotide

Octreotide is an inhibitor of the exocrine secretion of the pancreas. It has an anti-inflammatory action, reduces the pressure in the sphincter of Oddi and inhibits neural stimulation. Small studies have suggested a dose dependent effect with slightly better results in the highest dosing (200 µg) group. This difference was not clinically significant [28].

### Antioxidants

The observation that patients with chronic pancreatitis show low plasma levels of antioxidants. It is hypothesized that free radicals play a role in pancreatic injury. Administration of antioxidants seemed to be promising in animal models. These findings could however not be confirmed in human studies [46, 47].

### Non-pharmacological

The use of non-pharmacological treatment options is based on the anatomical origin of pain.

### Gastroenterological

#### Endoscopy

Endoscopic therapy is considered as first choice in uncomplicated chronic pancreatitis.

If the pancreatitis is induced by intraductal *stones*, extracorporeal shock wave lithotripsy is recommended, combined with endoscopic extraction of the stones. This was confirmed in a systematic review on 1,149 patients with success in 89 % [48]. Best results are obtained if stones are located in the head of the pancreas and in case of solitary stones. A morbidity is described of 6 % [48].

If the pancreatitis is caused by *strictures* of the main duct, stenting with endoscopic drainage is the therapy of choice according to the guidelines of the European Society of Gastrointestinal Endoscopy (ESGE) [49]. Strictures may be single or multiple. Depending on the size of dilatation of the main pancreatic duct behind the stricture, they are divided into dominant or non-dominant strictures (size >6 mm) and stenting can be performed by plastic or self-expandable metallic stents.

The technical success rate of stenting is high with an immediate pain relief in more than 65 % of the cases. During follow up of 14–58 months, this pain relief is ongoing in 32–68 % of the patients.

Pancreatic sphincterotomy should be performed prior to any stricture treatment [50–52].

*Pancreas Pseudocysts* are collections of pancreatic fluid surrounded by fibrous granulation tissue. These cysts can be drained by tubing transmural to the digestive wall or through the papil on EUS guidance. This is indicated if the cysts are enlarging or infected or in case of intracystic hemorrhage.

In case of clinical signs like pain, gastric outlet obstruction, weight loss, jaundice or early satiety, vascular compression of pancreaticopleural fistula drainage is indicated. Endoscopic drainage is the first choice therapy. It has a low cost with similar effects as surgery.

After 6–8 weeks, re-evaluation is performed and further treatment should be discussed multidisciplinary with endoscopists, surgeons, internists, radiologists, and pain specialists [53].

### Biliary Strictures

Up to 20 % of the chronic pancreatitis cases are related to biliary strictures. Treatment is necessary in case of elevated alkaline phosphatase and serum bilirubin for more than a month, biliary cirrhosis, stones or progression of biliary strictures.

Biliary obstruction complicates the course of chronic pancreatitis in 3–23 % of patients [54].

Different cholangiographic types of chronic pancreatitis-related biliary strictures have been described, the type being suggestive of the etiology of biliary obstruction (fibrosis, compression by a pseudocyst or cancer); therefore cancer should always be excluded by a brush cytology or PET scan [48].

### Surgery

Surgery is often performed when medical and endoscopic treatment did not provide satisfactory pain relief, or to exclude neoplasm and complications in the surrounding organs.

Pain can be treated by means of various techniques involving drainage (Puestow procedure) or resection (pancreaticoduodenectomy, total pancreatectomy with autotransplantation of the islets of Langerhans) or a combination of both (Frey procedure). Drainage procedures intend to reduce the pain by decompression of the pancreatic duct. The theory behind pain relief due to resection is that inflammatory activity causes pain as a result of qualitative and quantitative changes of the nerve fibers.

### Endoscopy Versus Surgery

The current guidelines for the management of pain due to chronic pancreatitis, recommend a step up approach, starting with lifestyle changes, pharmacological treatment including opioid analgesics and when these treatments provide insufficient effect, the endoscopic interventions are performed. Surgery is considered the last resort [26].

The choice between surgical or endoscopic treatment is difficult. Comparative studies do not provide exclusion on this point. In a 5-year follow up study, pain relapsed in 15 % in endoscopic treatment and 34 % in surgical treatment [49].



Recent studies have shown that preoperative opioid use predisposes to failure of long-term pain relief after surgical or endoscopic interventions. Peripheral and central sensitization is a possible explanation for this phenomenon [55, 56].

Although the European Society for Gastro-Enterology (ESGE) recommends endoscopic therapy as the first-line therapy for painful uncomplicated chronic pancreatitis, there is growing evidence that early surgical interventions have a better outcome concerning hospital stay, subsequent interventions, and relapse free interval with similar complication rates. Early surgical interventions give better pain relief but also better conservation of exocrine and endocrine function. Two recent randomized studies show that these surgical procedures lead to better results compared with endoscopic treatment [57, 58]. The percentage of patients who are free of pain after 5 years is 40 %.

The reluctance of gastroenterologist for surgery might be due to the high morbidity and mortality associated with pancreatic surgery in the setting of chronic pancreatitis. In contrast, morbidity and mortality rates for endoscopic therapy for chronic pancreatitis are rather low [48, 53, 58, 59].

## Ablative and Neuromodulation Techniques

Nerve blocks, ablative procedures, and neuromodulating techniques aim at interrupting or alternating the pain conduction. The neuro-anatomy is therefore important.

### Relevant Neuro-Anatomy

The sympathetic innervation of the abdominal organs starts from the anterolateral horn in the spinal cord. Preganglionic fibers of Th5–Th12 leave the spinal column after merging with the ventral ramus. Together with these communicating rami they course in the direction of the sympathetic chain. The fibers do not form synapses in the sympathetic chain, but run through it. The formation of synapses occurs more peripheral to the level of the ganglia: celiac ganglion, aorticorenal ganglion, superior mesenteric ganglion.

Preganglionic nerves confluence into three splanchnic nerves (greater, lesser, lowest) that course along the paravertebral border (Table 9.2).

Just below the level of the crus of the diaphragm, the splanchnic nerves confluence with the vagal preganglionic parasympathetic fibers, sensory fibers of the phrenic nerve,

and postganglionic sympathetic fibers to the celiac plexus that are draped around the abdominal aorta, especially at the anterior side. Figure 9.2 provides an image of the innervation of abdominal organs.

The splanchnic nerves are localized in a narrow pyramid of which the medial edge is formed by the lateral border of the vertebra, the lateral edge by the medial pleura and the crus of the diaphragm forms the basis of the triangle. The anterior side is formed by the posterior wall of the mediastinum and the posterior wall by the attachment of the parietal pleura on the lateral wall of the vertebrae [26].

## Nerve Blocks

### Celiac Plexus Block

Nerve blocks are widely used to reduce pain due to pancreatic cancer and pancreatitis. In patients with cancer, lysis (alcoholization or phenolization) of the celiac plexus has a positive recommendation [60]. Injection of a neurolytic agent around the nerve has several risks, such as uncontrolled flow of the neurolytic and uncontrolled lesion size. Using a neurolytic agent around the celiac plexus may cause paraplegia and retroperitoneal fibrosis. Therefore the use of neurolytic agents is restricted to the management of patients with cancer. Injection of local anesthetics, steroids, and antibiotics was recommended instead, based on the idea of decreasing neuronal inflammation [61]. Even for a chronic disease state as pancreatitis, the reported experiences do not present long-term effects [62]. The effect is not prolonged in time if repeated blocks are performed.

### Techniques

Most of the Celiac Plexus Block (CPB) is performed percutaneous under fluoroscopic guidance. Transaortic and retrocrural techniques are described with both paravertebral and transdiscal approaches.

### CT Guided

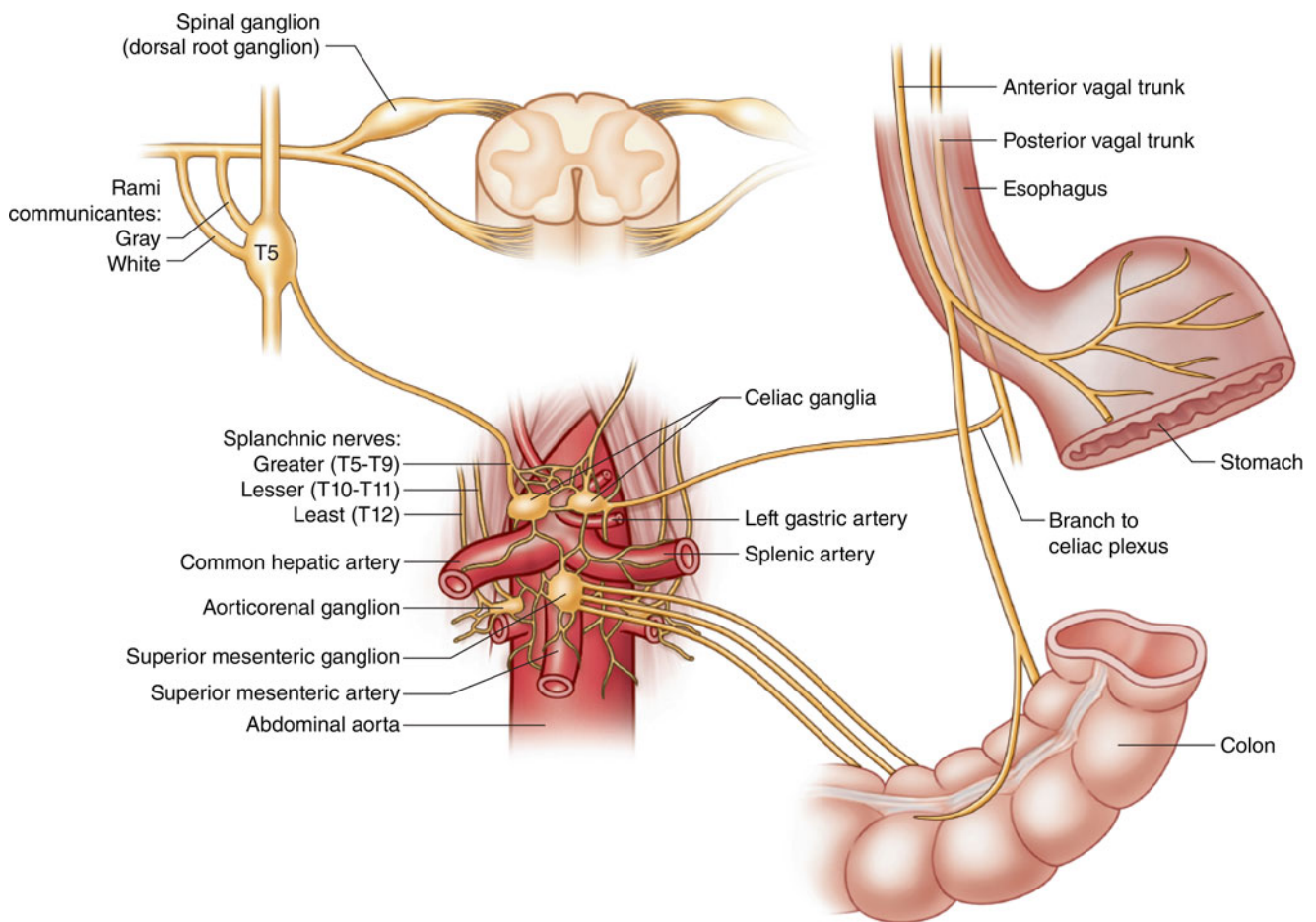
CT allows excellent visualization of the anatomic structures that lie in close proximity to the target site during neurolytic CPB. Performing the procedure this way might avoid complications such as hematuria, intravascular injection, and pneumothorax [63].

### Ultrasound Guided

The introduction of endoscopic ultrasound led to the ultrasound guided celiac plexus block (with local anesthetic and corticosteroid) or celiac plexus neurolysis [64]. A prospective study on the efficacy and safety of endoscopic ultrasound guided celiac plexus block showed good pain relief in 55 % of the patients at 4 and 8 weeks follow-up.

**Table 9.2** Splanchnic nerves and preganglionic fiber level

Splanchnic nerve division	Preganglionic fiber level
Greater splanchnic nerve	Th5–Th9
Lesser splanchnic nerve	Th10–Th11
Lowest splanchnic nerve	Th11–Th12



**Fig. 9.2** Innervation of the abdominal organs. Modified from Rogier Trompert, Medical Art

At 12 and 24 weeks follow-up, 26 and 10 % of patients respectively had ongoing pain relief [65].

Complications of endoscopic ultrasound guided celiac plexus block and neurolysis were studied in a large series of prospectively collected information. The overall complication rate was 1.8 %; only one major complication occurred in the neurolysis group [66]. Recently case reports on spinal cord infarction after the endoscopic procedure with major complications, such as paraplegia, were published [67, 68].

### Splanchnic Nerve Block

The specific anatomy in which the splanchnic nerves are located in a narrow compartment allows a targeted denervation. Radiofrequency (RF) thermolesioning, in which denervation only takes place at the tip of the electrode, seems more suitable than injection of neurolytics for this indication.

The use of RF nervus splanchnicus treatment has been described in two patient series [69, 70]. Raj [69] reports on 107 patients who underwent RF treatment of the splanchnic

nerves as a treatment of upper abdominal pain. The involvement of the splanchnic nerves was confirmed by means of a diagnostic block with a local anesthetic. Seventy-three patients were followed prospectively. Thirty-eight patients only received a block with a local anesthetic and 31 received RF treatment. In both groups a pain relief of >50 % was found in 40 % of the patients.

Garcea [70] describes ten patients who underwent RF splanchnic nerve denervation as a treatment of chronic pancreatitis with a mean follow-up of 18 months (12–24 months). A significant pain reduction was observed, accompanied by a clear decrease in the need for opiates and acute hospitalization. Moreover, the parameters of the quality of life improved as well.

A recently published retrospective review of patients with chronic pancreatitis treated with RF thermolesioning of the splanchnic nerve showed a significant pain reduction for a mean period of 45 weeks in 11/18 patients. The analgesic use was significantly reduced in 4 patients and 4 other patients stopped completely analgesic intake [71]. In the patients that had a good pain relief, the procedure could be repeated in

case of relapse and the effect was comparable. Presumably the pain returns due to nerve regeneration.

Complications of RF thermolesioning of the splanchnic nerve cannot be derived from the small series published up till now. As with the neurolytic blocks, postprocedural neuritis is possible. Hypotension and diarrhea may occur shortly after the intervention, but can be treated easily.

The use of pulsed radiofrequency of the splanchnic nerve was described in two cases by Brennan et al. [72]. The effect of this treatment needs further study in large patient groups.

### Thoracoscopic Splanchnicectomy

The nociceptive fibers from the pancreas are incorporated in the splanchnic nerves. By transecting these nociceptive fibers, a long-term pain relief was expected.

Recent advances in laparoscopic techniques formed new developments in the field of thoracoscopy. The first report on successful thoracoscopic splanchnicectomy for pancreatic pain was published in 1993. This procedure is performed under general anesthesia with double lumen intubation and one lung ventilation in prone position. With this thoracoscopic operation technique, dissection of the parietal pleura was performed from Th5 till Th10 to identify and transect the nociceptive splanchnic nerve fibers at the thoracic level. This technique was promising because of sufficient pain relief with maintenance of the pancreatic function. In some cases the transection was uncertain and this resulted in a fast recurrence of pain.

Early pain relief was significant in several studies but after 6 months, there was recurrence in 25 % of the patients. Pain recurred in 50 % of the patients followed for a long term.

Bilateral thoracoscopic splanchnicectomy appears to work best in patients who have had no prior operative or endoscopic interventions. Prior opioid abuse results in reduced efficacy.

Other nerve structures may take over nociception. The vagal nerve was presumed to be a partner for this transmission, but, additional vagotomy does not give any additional effect. Due to sensitization, inactive nociceptors can become activated due to certain stimuli and play an active role in chronic visceral pain [73–77].

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### Spinal Cord Stimulation

The use of Spinal Cord Stimulation (SCS) to treat visceral pain was initially described in several case reports [78–83]. A recent publication of a retrospective review of 35 patients who received a trial with SCS reported that 30 % experienced  $\geq 50$  % pain relief at the end of the trial [84]. In the 28 patients who received a permanent implant, 1 was lost to follow-up and 5 had the lead and generator removed

for various reasons. Nineteen of the 22 patients were followed for more than 1 year. Over the complete evaluation period pain scores and opioid use remained low, suggesting that SCS for chronic abdominal pain of various causes may provide consistent long-term improvements. A national survey on SCS for chronic abdominal pain that followed this retrospective study included 76 case reports and its results were consistent in technical aspects of SCS implantation, as well as the opioid use and pain score improvements [84, 85]. Both studies described SCS leads positioned with their tips mostly at the level of Th5 vertebral body. Pain relief exceeded 50 % in most of the patients and long-term opioid use decreased by more than 2/3 [84, 85]. Another interesting fact from both studies is the presence of the large treated population of the patients with severe chronic pancreatitis [84, 85]. There were 26 out of 35 patients in a retrospective, and 26 out of 70 patients in survey study who had diagnosis of chronic pancreatitis. Analyzed effects of SCS in this subgroup of the patients helped to conclude that the improvements in opioid use and pain scores were similar to those of patients with other sources of their chronic visceral abdominal pain.

In a retrospective analysis 30 patients with severe pain due to chronic pancreatitis underwent a trial with spinal cord stimulation during 7–14 days. Twenty-four patients reported 80 % pain relief at the end of the trial period. After definite implantation 1 patient was lost to follow-up and in 3 patients the system had to be removed because of infection. At 1-year follow-up VAS score pain and opioid consumption were significantly reduced [86].

The main complications of SCS are migration and breakage of the electrode. In addition infection which includes anything from cellulites to epidural abscess is possible.

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### Splanchnic Nerve Stimulation

A case report of a young patient with painful chronic pancreatitis of more than 5 years duration and refractory to all conservative treatments illustrates a considerable pain reduction, and diminished opioid consumption for at least 18 months was obtained with neuromodulation of the splanchnic nerves with two permanently implanted octopolar leads at the Th11/Th12 area connected to an implantable pulse generator [87]. This experimental treatment may be further investigated.

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### Conclusion

Pain due to chronic pancreatitis is severe and reduces the quality of life tremendously. At this moment, treatment is partially dependent on the medical specialists that look to the problem.

Better understanding of the potential mechanisms of pain can elucidate the effect or ineffectiveness of current therapy and result in the development of better treatment options. Resection or decompression of ductal stenosis will have no impact on the hypersensitivity of the gland. Ineffectiveness of neuro-ablative procedures can be an anatomical issue but also due to regeneration of nerve fibers with secondary extra input to the cord. Another important issue is the central sensitization which is a strong indication for spinal cord stimulation.

Comparative studies between surgery and endoscopic treatment show evidence in favor of early surgery.

When establishing a pharmacological pain treatment, non-analgesic drugs should also be considered. Antiepileptic drugs type Ca channel blocking agents seem to be effective. Other potential targets in the treatment are NGF inhibitors, TRPV1 antagonist. Concerning the central sensitization, the NMDA receptor blocking agents might play an important role but at this moment, they are impracticable because of the narrow therapeutic window and administration difficulties.

Studies on nerve blocks mainly focus on the CPB, which should be reserved for the treatment of cancer patients. Radiofrequency treatment of the splanchnic nerves seems promising but further RCT is needed to confirm the effect. These blocks could reduce pain to an extent that surgery can be delayed or even prevented.

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