EVIDENCE-BASED MEDICINE

Evidence-Based Interventional Pain Medicine
According to Clinical Diagnoses

26. Pain in Chronic Pancreatitis

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■ **Abstract:** Chronic pancreatitis is defined as a progressive inflammatory response of the pancreas that has lead to irreversible morphological changes of the parenchyma (fibrosis, loss of acini and islets of Langerhans, and formation of pancreatic stones) as well as of the pancreatic duct (stenosis and pancreatic stones). Pain is one of the most important symptoms of chronic pancreatitis. The pathogenesis of this pain can only partly be explained and it is therefore often difficult to treat this symptom.

The management of pain induced by chronic pancreatitis starts with lifestyle changes and analgesics.

For the pharmacological management, the three-step ladder of the World Health Organization extended with the use of co-analgesics is followed.

Interventional pain management may consist of radiofrequency treatment of the nervi splanchnici, spinal cord stimulation, endoscopic stenting or stone extraction possibly in combination with lithotripsy, and surgery.

To date, there are no randomized controlled trials supporting the efficacy of radiofrequency and spinal cord stimulation. The large published series reports justify a recommendation to consider these treatment options. Radiofrequency treatment, being less invasive than spinal cord stimulation, could be tested prior to considering spinal cord stimulation.

There are several other treatment possibilities such as endoscopic or surgical treatment, pancreatic enzyme supplementation and administration of octreotide and antioxidants. All may have a role in the management of pain induced by chronic pancreatitis. ■

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INTRODUCTION

This review on chronic pancreatitis is part of the series ''Evidence-based Interventional Pain Medicine according to clinical diagnoses.'' Recommendations formulated in this chapter are based on ''Grading strength of recommendations and quality of evidence in clinical guidelines'' described by Guyatt et al.,[1] and adapted by van Kleef et al.[2] in the editorial accompanying the first article of this series (Table 1). The latest literature update was performed in September 2010.

The pancreas consists of acini, islets of Langerhans, and ducts. Acini are units of approximately 20 acinar cells with a few centroacinar cells. Several pancreatic enzymes are produced in the acinar cells: amylase in an active form, lipases, nucleases, and proteolytic enzymes (trypsins) in an inactive form. The centroacinar cells produce bicarbonate. The A cells in the islets of Langerhans produce glucagon and the B cells insulin. The regulation of the pancreas is controlled by hormones and the autonomic (sympathetic and parasympathetic) nervous system. The hormone cholecystokinin (CCK) is released from special intestinal cells and has a stimulating effect on the exocrine function of the pancreas. The release of CCK is stimulated by CCK-releasing peptide, a protein that is intraluminally active and denatured by trypsin.

Innervation of the pancreas consists of sympathetic fibers from the nervi splanchnici and parasympathetic fibers from the nervi vagi. The intrapancreatic acinar plexus contains both sympathetic and parasympathetic fibers. Parasympathetic fibers stimulate exocrine as well as endocrine secretion. Sympathetic fibers mainly have an inhibiting effect on this release. A rich sensory network is located in the pancreas around the acinar cells.[3–5]

Chronic pancreatitis is defined as a progressive inflammatory response of the pancreas that leads to irreversible morphological changes of the parenchyma (fibrosis, loss of acini and islets of Langerhans, and the formation of pancreatic stones), as well as the pancreatic duct (stenosis and pancreatic stones).

In contrast to acute pancreatitis, in which the acute inflammatory damage is transient, chronic pancreatitis involves a progressive process. Although these two clinical pictures may overlap (recurrent episodes of acute pancreatitis may lead to chronic pancreatitis), they each have a different pathological picture, etiology, and course.[6]

Also in contrast to acute pancreatitis, which involves a neutrophilic inflammatory reaction, chronic pancreatitis is characterized by mononuclear infiltration and fibrosis. Fibrosing of the parenchyma accompanied by the loss of acini and islets of Langerhans eventually leads to loss of function. This functional loss can be both exocrine (resulting in lipase deficiency with steatorrhea, diarrhea, and weight loss) and endocrine (causing diabetes mellitus [DM] in case of insulin

Table 1. Summary of Evidence Scores and Implications for Recommendation

Score	Description	Implication
1A+	Effectiveness demonstrated in various RCTs of good quality. The benefits clearly outweigh risk and burdens	Positive recommendation
1B+	One RCT or more RCTs with methodological weaknesses, demonstrate effectiveness. The benefits clearly outweigh risk and burdens	
2B+	One or more RCTs with methodological weaknesses, demonstrate effectiveness. Benefits closely balanced with risk and burdens	
2B±	Multiple RCTs, with methodological weaknesses, yield contradictory results better or worse than the control treatment. Benefits closely balanced with risk and burdens, or uncertainty in the estimates of benefits, risk and burdens	Considered, preferably study-related
2C+	Effectiveness only demonstrated in observational studies. Given that there is no conclusive evidence of the effect, benefits closely balanced with risk and burdens	
0	There is no literature or there are case reports available, but these are insufficient to prove effectiveness and/or safety. These treatments should only be applied in relation to studies	Only study-related
2C−	Observational studies indicate no or too short-lived effectiveness. Given that there is no positive clinical effect, risk and burdens outweigh the benefit	Negative recommendation
2B−	One or more RCTs with methodological weaknesses, or large observational studies that do not indicate any superiority to the control treatment. Given that there is no positive clinical effect, risk and burdens outweigh the benefit	
2A−	RCT of a good quality which does not exhibit any clinical effect. Given that there is no positive clinical effect, risk and burdens outweigh the benefit	

RCT, randomized controlled trial.

deficiency). This functional loss only occurs when 90% of the acini or islets of Langerhans are lost, respectively. Moreover, the fibrosing process can lead to strictures in the structures next to the pancreas, such as the duodenum, ductus choledochus, and colon. Fibrosis around the vena lienalis can cause thrombosis of this vein, eventually resulting in hemorrhages from gastric (fundal) varices. Morphological changes of the ductus pancreaticus may lead to a rupture resulting in pseudocysts, ascites, and fistulas. Two to three per cent of the patients with chronic pancreatitis ultimately develop a pancreatic carcinoma. The most common symptoms, however, are exocrine pancreatic insufficiency and pain.[7–10]

EPIDEMIOLOGY

The incidence of chronic pancreatitis in the Western world amounts to 10/100,000. It is more common in men (3:1), and presents mostly between ages 40 and 50. Chronic pancreatitis cannot be cured. Ten years after the disorder has been diagnosed, 30% of the patients will have died. Death rarely results from multiple organ failure or sepsis in case of an acute exacerbation, surgical complications or late complications of DM. It is more likely that premature death is caused by the patient's lifestyle. These patients have an increased risk to develop lung cancer or esophageal cancer as a result of nicotine and alcohol abuse. In addition, they have an increased risk of cardiovascular disease and alcohol-related accidents. Finally, these patients have an increased risk to develop a pancreatic carcinoma.[11–13]

ETIOLOGY

Chronic pancreatitis is associated with (excessive) alcohol use in 70% to 80% of the patients. The mechanism of how alcohol causes pancreatitis is not yet clear. A large number of alcoholics do not develop pancreatitis, so a genetic factor may also be involved. It has been difficult to unravel the mechanism that causes alcohol-associated pancreatitis because there is no animal model in which the symptoms can be reproduced to simulate human alcoholic pancreatitis. It has been possible, however, to use animal models to show that alcohol increases the severity of pancreatitis that has been induced in another way.[14]

Alcohol does not play a role in 30% of the patients. In approximately half of these patients, the etiology can be established (Table 2); the other patients are considered to have idiopathic chronic pancreatitis.[15]

Table 2. Possible Etiologies of Chronic Pancreatitis

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

Pain is one of the most important symptoms of chronic pancreatitis. The pathogenesis of this pain can only partly been explained and it is therefore often difficult to treat this symptom. Pain in pancreatitis may be caused by different mechanisms.

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

Nociceptive pain occurs after the activation of primary afferent neurons that respond to a 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.[16] 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.[17]

One theory argues that high pressure in the ductus pancreaticus leads to pain due to obstruction. Obstruction of the ductus pancreaticus can cause an ''overpressure'' proximally. This explanation of the pain is the basis for endoscopic and surgical drainage procedures. In 1970, an article was published about a patient in whom pain could be induced by injecting salt solutions in a drainage catheter located in a pancreatic fistula.[18]

Subsequently, several studies into overpressure in the ductus pancreaticus were carried out (preoperatively and during endoscopic retrograde cholangio pancreatography with manometry of the ductus pancreaticus), 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 after the procedure, there was no consistent correlation with the pain.[19–21]

Other factors that may cause nociceptive pain in chronic pancreatitis include: obstruction of the duodenum or 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.[22,23]

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 ganglia spinalia (dorsal root ganglia).[24] Patients with chronic pancreatitis appear to show generalized hyperalgesia, possibly based on deep sensitization.[25]

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.[26]

I. DIAGNOSIS

I.A HISTORY

Patients with chronic pancreatitis can be free of pain for long periods of time (acute pancreatitis is always painful). This occurs in 20% of the patients with chronic pancreatitis and exocrine pancreatic insufficiency. These patients mainly suffer from diarrhea, foul-smelling stools that are difficult to flush (floating) and weight loss. Steatorrhea may lead to deficiencies of fat-soluble vitamins (A, D, E, and K) and vitamin B12. Also, chronic pancreatitis can cause insulin-dependent DM. This usually occurs later in the course of the disease. The risk of developing early DM appears to be increased in patients with a positive family history for DM and in patients with chronic pancreatitis and multiple pancreatic calcifications upon imaging. As the production of glucagon is disturbed in chronic pancreatitis, this form of DM includes a higher risk of hypoglycemia. Diabetic ketoacidosis and nephropathy are rare, but neuropathy and retinopathy are very common.[8,27,28]

Patients with pain typically complain of epigastric pain that radiates through to the back. The pain may deteriorate 20 to 30 minutes after a meal and is often accompanied by nausea and vomiting. Two patterns of symptoms are described in patients with alcoholic chronic pancreatitis. Type I is pain presenting in episodes of one to several weeks duration with pain-free intervals that can last for months or years. Type II is persistent pain with exacerbations requiring hospitalization.[29]

I.B PHYSICAL EXAMINATION

Physical examination usually does not reveal more than pain with pressure applied to the epigastrium.

Fever or a palpable mass suggests a complicated course of chronic pancreatitis (pseudocyst).

I.C ADDITIONAL TESTS

Because the pancreas is not encapsulated, acute pancreatitis can spread rapidly in a normal pancreas from parenchymal edema via surrounding fat (fat necrosis) to the retroperitoneal areas. In case of a chronically inflamed pancreas, a possible additional acute inflammatory component may be limited to a small area due to fibrosis of the pancreas. Therefore, routine laboratory examination does not play an important role in the diagnosis of chronic pancreatitis because amylase, lipase, and inflammatory parameters can be completely normal or only slightly elevated.[30]

A decreased exocrine function due to chronic inflammation can be demonstrated by means of a determination of elastase and fecal fat excretion. Glucose/HbA1c determination can be used to assess the endocrine pancreatic function. In case of chronic pancreatitis, the exocrine function is usually affected sooner and more severely than the endocrine function.[31]

Imaging techniques that may contribute to the diagnosis of chronic pancreatitis include: ultrasound, CT, MRI, and endoscopic ultrasound (EUS). The diagnosis is established by means of imaging and functional evaluation. Ultrasound and CT can be used to demonstrate abnormalities in the pancreatic parenchyma, such as

calcifications, pseudocysts, and tumors. Magnetic resonance cholangio pancreatography examination can show abnormalities in the ductus pancreaticus, such as strictures, dilatations, and intraductal concrements. If the diagnosis of pancreatitis is doubted, EUS can be used to perform a puncture of the focal lesions or cysts to exclude malignancies.[32–36]

I.D DIFFERENTIAL DIAGNOSIS

1. Pancreatic carcinoma
2. Peptic ulcer
3. Symptomatic gallstone disease
4. Irritable bowel syndrome

II. TREATMENT OPTIONS

II.A CONSERVATIVE MANAGEMENT

Causal Treatment

The following symptoms and complications of chronic pancreatitis should be treated first.[37–39]

- Pseudocysts, if they are causing pain because of their location or if their size increases. Treatment: endoscopic, radiological or surgical drainage.
- Obstruction of the ductus choledochus. Treatment: endoscopic stenting or surgical choledochoenterostomy.
- Duodenal obstruction with passage problems. Treatment: gastrojejunostomy.

The initial treatment of pain in chronic pancreatitis consists first of all of lifestyle adjustments and analgesics.

Lifestyle Adjustments

In view of the association between alcohol abuse and pancreatitis, total abstinence from alcohol is recommended (also in patients with chronic pancreatitis in whom another etiology has been found). This may result in pain reduction, and in better survivalrates.[8,40,41] However, there are no prospective randomized studies or systematic reviews that prove this assertion.

Analgesics

All treatment guidelines for pain in chronic pancreatitis follow the 3-step ladder of the World Health Organization for the treatment of chronic pain.

The treatment should start with monotherapy. If this has insufficient effect, a combination therapy can be applied. Peripherally acting medication is then combined with centrally acting medication.

The first step in cases of limited-to-mild pain consists of nonopioid analgesics. The second step is applied in cases of mild-to-moderate pain and combines a nonopioid analgesic with a weak opioid. Titration is performed until the result is satisfactory. In cases of severe pain, a strong opioid such as morphine is prescribed (Step 3). The three steps can be combined with co-analgesics: an antiepileptic or a tricyclic antidepressant drug.

There are no randomized studies that compare the efficacy of the analgesics mentioned above for the treatment of pain in chronic pancreatitis. It is important to prescribe long-acting instead of short-acting morphinomimetics because of the tendency of this patient group to become addicted. It is also essential to register the effect of pain medication, for example by means of the visual analog score. The pain medication should preferably be prescribed by only one doctor to monitor the effect and reduce the risk of doctor-shopping behavior and addiction.

Paracetamol. Paracetamol (acetaminophen) is the pain medication of first choice. It has good analgesic and antipyretic properties and few side effects, especially no gastrointestinal side effects in the recommended dosage. However, paracetamol does not have any activity on cyclooxygenase (COX) and thus no anti-inflammatory activity.

Nonsteroidal Anti-Inflammatory Drugs. The mechanisms of pain in chronic pancreatitis described above (nociceptive pain, neuropathic pain, and neurogenic inflammation) justify the prescription of anti-inflammatory analgesics. Nonsteroidal anti-inflammatory drugs (NSAIDs), compared to the prototype aspirin, exert COX-1 and COX-2-inhibiting activity in varying degrees. Therefore, they possess a pain-relieving, antipyretic as well as anti-inflammatory activity. NSAIDs are therefore considered the first choice for nociceptive pain. Theoretically, NSAIDs can also play a positive role in reducing neurogenic inflammation.

However, the possible advantages of NSAIDs should be weighed against the disadvantages compared to, for instance, paracetamol. The side effects of NSAIDs vary from dyspepsia and skin disorders to gastric ulcerations and renal toxicity. Renal toxicity

depends especially on the glomerular filtration rate. This implies that patients with renal disorders, liver cirrhosis and heart failure have an increased risk of nephrotoxicity. Risk factors for gastrointestinal side effects include: advanced age, liver cirrhosis, and additional factors that influence coagulation. If NSAIDs are chronically prescribed, it is generally recommended to add a proton pump inhibitor to the therapy.

Selective COX-2 Inhibitors. Recent data show overexpression of COX-2 in chronic pancreatitis.[42] 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, and they are therefore not indicated in the treatment of chronic pancreatitis. There are case reports that suggest COX-2 inhibitors induce flares of acute pancreatitis.

Opioids. If NSAIDs do not result in sufficient pain relief, opioids can be prescribed. Long-acting preparations are preferred. If necessary, a fast-acting morphine preparation can be prescribed. Nausea and vomiting may occur when these preparations are started, but the side effects will soon disappear and can be treated with low doses of a centrally acting antiemetic or haloperidol. In cases of constipation caused by medication, laxatives can be added to the therapy. Opioids therapy might be controversial in chronic pancreatitis patients as there is often a coincidence with addiction.

Opioids are active by binding to one of the known opioid receptors (mu, kappa, and delta). Opioid receptors are also present in the sphincter of Oddi. The sphincter of Oddi 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 (μ-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.[43–46]

Patients with chronic pancreatitis often suffer from depression due to their chronic pain symptoms. Tricyclic antidepressants have an effect on neuropathic pain as well as on depressive symptoms and can therefore contribute substantially to the treatment of pain in chronic pancreatitis.

Anticonvulsive drugs, gabapentin in particular, appear to be effective in the treatment of neuropathic pain in DM. Gabapentin is now frequently prescribed in cases of chronic pain in pancreatitis.[46]

II.B INTERVENTIONAL MANAGEMENT

- Anesthesiological: radiofrequency (RF) treatment of the nervi splanchnici and spinal cord stimulation (SCS).
- Endoscopic: stenting, stone extraction possibly in combination with lithotripsy.
- Surgical.

Anesthesiological Pain Treatment

Relevant Anatomy. The sympathetic innervation of the abdominal organs starts from the anterolateral horn in the spinal cord. Preganglionar (preganglionic) fibers of Th5 to Th12 leave the spinal column after merging with the ramus ventralis. Together with these communicating rami they course in the direction of the truncus sympathicus (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: ganglion coeliacum, ganglion aorticorenale, ganglion mesentericum superius.

Preganglionar nerves confluence into three nervi splanchnici (major, minor, imus) that course along the paravertebral border (Table 3).

Table 3. Nervi Splanchnici and Preganglionair Fiber Level

Nervus Splanchnicus Division	Preganglionar Fiber Level
Nervus splanchnicus major	Th5 to Th9
Nervus splanchnicus minor	Th10 to Th11
Nervus splanchnicus imus	Th11 to Th12

Just below the level of the crus of the diaphragm, the nervi splanchnici confluence with the vagal preganglionar parasympathetic fibers, sensory fibers of the nervus phrenicus, and postganglionar sympathetic fibers to the plexus coeliacus that are draped around the aorta abdominalis, especially at the anterior side. Figure 1 provides an image of the innervation of abdominal organs.

The nervi splanchnici 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 pleura parietalis on the lateral wall of the vertebrae.

Nervus Splanchnicus Block

The specific anatomy in which the nervi splanchnici are located in a narrow compartment allows a targeted denervation. The use of neurolytic agents—in patients with nonmalignant pain—has gradually been abandoned because of possible complications. RF thermolesioning, in which denervation only takes place at the tip of the electrode, seems more suitable for this indication.

The use of RF nervus splanchnicus treatment has been described in two patient series.[47,48] Raj et al.[47] reported on 107 patients who underwent RF treatment of the nervi splanchnici as a treatment of upper abdominal pain. The involvement of the nervi splanchnici 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 et al.[48] described 10 patients who underwent RF nervus splanchnicus denervation as a treatment of chronic pancreatitis with a mean follow-up of 18 months (12 to 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.

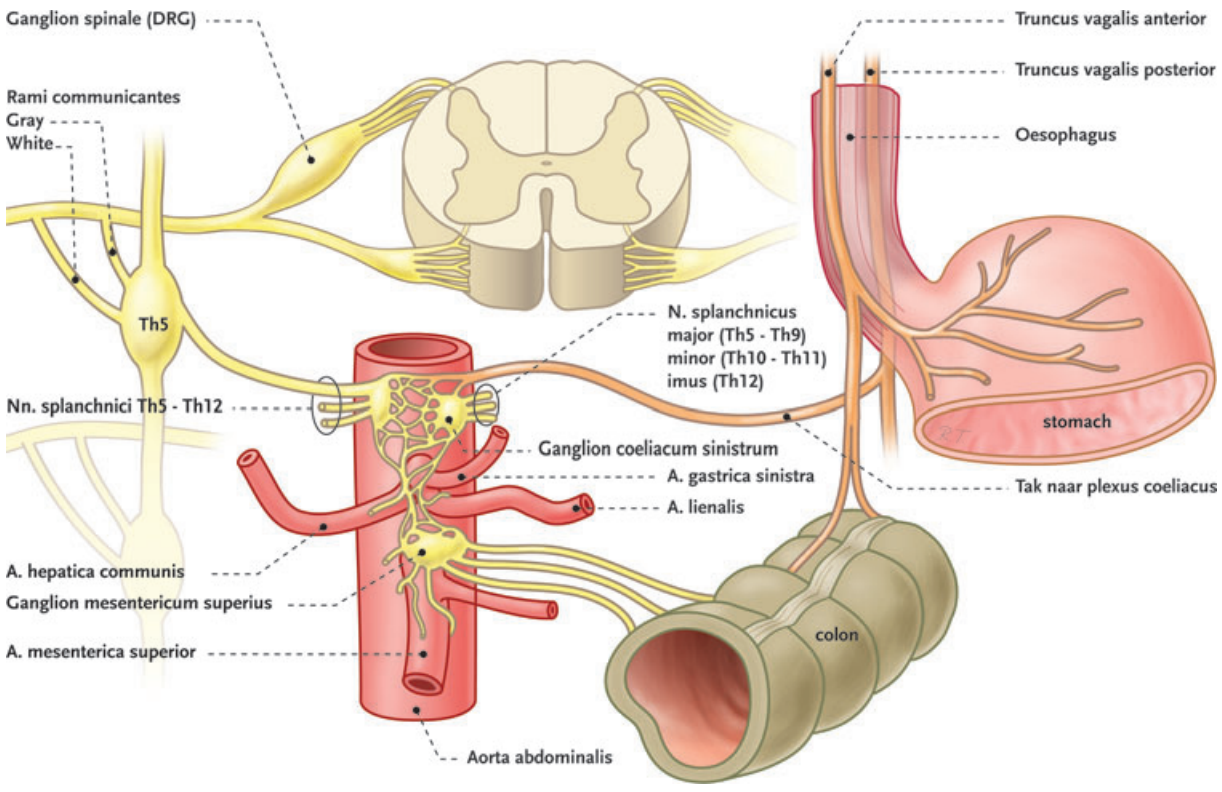

Figure 1. Innervation of the abdominal organs.

Spinal Cord Stimulation

The use of SCS to treat visceral pain was initially described in case reports.[49–54] A recent publication of a retrospective review of 35 patients who received a trial with SCS reported that 30% experienced ≥ 50% pain relief at the end of the trial.[55] In the 28 patients who received a permanent implant, one was lost to follow-up and five 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.[55,56] 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 two-thirds.[55,56] Another interesting feature noted in both studies is the presence of the large treated population of the patients with severe chronic pancreatitis.[55,56] There were 26 of 35 patients in a retrospective, and 26 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.

II.C COMPLICATIONS OF INTERVENTIONAL MANAGEMENT

Complications of RF Nervus Splanchnicus Block

The data available are insufficient to provide information about the incidence of complications. No major complications have been reported. Taking the information about neurolytic blocks into account, RF treatment can also induce postprocedural neuritis. This usually disappears within a few weeks and should be treated with medication. Hypotension and diarrhea may occur shortly after the intervention, but can be treated easily. As in all procedures at thoracic level, one should be alert to possible pneumothorax. A control radiograph of the thorax should therefore be made no more than 1 hour after the procedure. The patient may report a subjective feeling of dyspnea, which is attributed to a high position of the diaphragm, caused by the anesthetization of the nervus phrenicus.

Ductus thoracicus injury: upon aspiration a yellowish, turbid fluid is noted.

Intradiscal and intravascular injection: this should always be verified with a contrast.

Paresthesia: when contacting lumbar or thoracic roots.

Complications of SCS

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

II.D EVIDENCE FOR INTERVENTIONAL MANAGEMENT

The summary of the evidence for the interventional management of chronic pancreatitis is given in Table 4.

III. RECOMMENDATIONS

Radiofrequency nervus splanchnicus block can be considered in patients with chronic pancreatitis that is refractory to conventional treatment.

Spinal cord stimulation can be applied in the context of studies in patients with symptoms that cannot be treated by means of RF nervus splanchnicus block.

III.A CLINICAL PRACTICE ALGORITHM

Figure 2 represents the treatment algorithm for painful chronic pancreatitis based on the available evidence.

III.B TECHNIQUE(S)

Percutaneous RF Nervus Splanchnicus Treatment

The intervention is performed under X-ray guidance. The patient is placed in prone position on a translucent

Table 4. Summary of the Evidence for Interventional Management of Pain due to Chronic Pancreatitis

Technique	Assessment
Radiofrequency nervus splanchnicus block	2 C+
Spinal cord stimulation	2 C+

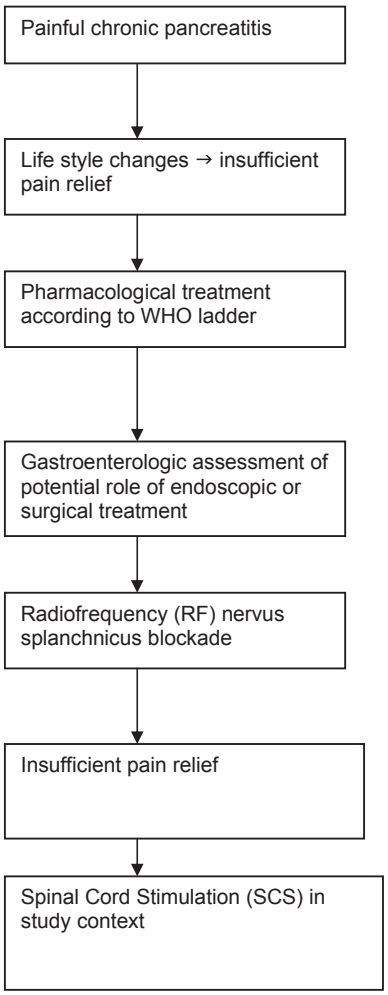

Figure 2. Treatment algorithm for chronic pancreatitis.

table with a pillow underneath the abdomen to reduce lumbar lordosis. Prior to the procedure, an intravenous infusion line is placed and an ECG and saturation monitoring are installed. Also, the patient is provided with 3 L/minute O_2 via nasal cannula. The procedure takes place under sedation with propofol or remifentanyl and spontaneous respiration.

Th12 and L1 are identified in a posteroanterior position and the vertebral endplates are aligned. The C-arm is rotated 5° to 10° to the side to be treated. The patient is asked to breathe in and out deeply. The attachment of the diaphragm is identified at mid-Th12 level. The needle placement site is located where the rib is attached to vertebrae Th11 and Th12, and above the diaphragm. The entry site is marked with a pen. The skin and the deeper layers are infiltrated with 5 mL of a local anesthetic (eg, lidocaine 2%) with a 22-G needle.

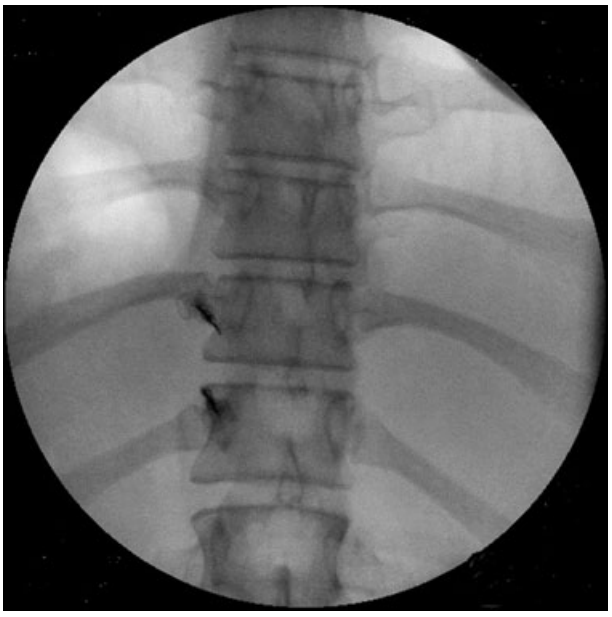

Figure 3. Radiofrequency nervus splanchnicus block at Th11 and T12 level: AP image.

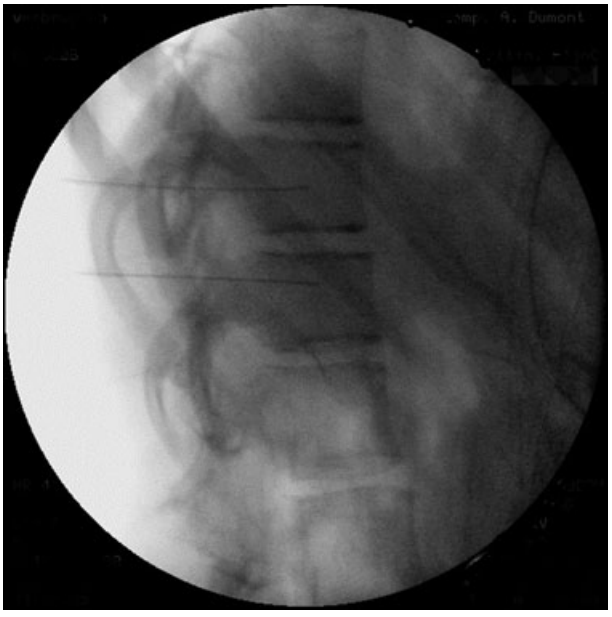

Figure 4. Radiofrequency nervus splanchnicus block at Th11 and T12 level: lateral image.

The treatment is performed with a 10- to 15-cm 22-G blunt or sharp curved needle with an active tip of 10 mm. As these patients are often very lean, a 10-cm needle is usually of sufficient length. The direction of the curve is visualized by a red dot at the hub of the needle. An intravenous 14-G catheter (as an introducer) is first inserted in perfect *tunnel view* aiming for a needle position just beside the corpus vertebrae.

When the catheter has been inserted two-thirds into the patient, the stylet is removed and the needle depth checked in lateral view. The needle must stay posterior to the foramen intervertebrale.

The C-arm is returned to the tunnel view. Subsequently, the RF cannula is inserted through the introducer. It is advanced maintaining the tunnel view. Initially, the bent tip of the needle is turned outwards to prevent needle passage into the foramen intervertebrale. Once the needle has passed beyond the foramen, it is turned such that the curve faces medially to maintain close contact with the corpus vertebrae. The needle depth is regularly monitored (every 0.5 cm) in lateral view of the fluoroscopy. The final position of the needle tip is against the corpus vertebrae at the junction between the anterior and middle one-third of the vertebra (Figures 3 and 4). It should also be regularly checked as to whether any blood, cerebrospinal fluid (CSF) or chyle appears from the needle depending on the catheter depth. If any CSF or chyle is noticed, the procedure should be discontinued and a new session can be considered a few days later.

One milliliter of nonionic, non-neurotoxic contrast fluid (iohexol) is injected. The needle is located in posteroanterior view just over the lateral vertebral edge. The contrast should show an overlapping sausage-shaped image between the thoracic vertebrae over the lateral vertebral edge. The contrast fluid will fan out in case of an intrapleural location.

Initially, a diagnostic block will be performed by injecting bupivacaine 0.5% 3 mL (up to 5 mL). Higher volumes result in an increased incidence of false-positive blocks. This can also lead to additional anesthesia of the nervus phrenicus, which may cause an elevation of the diaphragm with secondary respiratory problems.

If the diagnostic block had positive results, RF treatment can be performed at a second session. The needle is positioned at the same location under fluoroscopic control. Once a good location is verified in tunnel vision and lateral view, the needle position is then also checked by electrical stimulation.

The RF device is connected to the needle and a grounding plate applied to the patient. The impedance should be lower than 250 Ω. The patient will feel a vibrating epigastric sensation at 50 Hz and a threshold of < 1 V. If the electrical sensation is noted in the intercostal area, the needle should be moved further ventral. In addition, motor stimulation is applied at 2 Hz, focusing mainly on intercostal stimulation. Normally, no stimulation is felt.

If the test results are positive, local anesthetics are administered (2 to 3 mL of lidocaine 2% or bupivacaine 0.5%). The RF treatment can be carried out after several minutes. The needle position is monitored in the lateral view. For each level, the treatment consists of three 90-second cycles at 80°C. The needle is first turned with its curve in cranial direction, then neutral, and finally in caudal direction as a maximum area can thus be treated.

Spinal Cord Stimulation

The technique for SCS is described in the article on CRPS of this series.[57]

IV. OTHER TREATMENT OPTIONS

IV.A ENDOSCOPY

It is possible to bypass endoscopic obstructions of the ductus pancreaticus due to stones or stenosis. It is important in this respect to realize that no correlation has been shown between pain and the presence of intraductal stones nor are there any guidelines stipulating which degree of obstruction justifies or requires endoscopic intervention. Three recent studies into the effect of pancreatic stenting, either alone or combined with lithotripsy and/or sphincterotomy, showed a decrease of the pain[58,59] or no effect.[60] The effect of therapy on pain is often good in the short term, but soon decreases. Five years after endoscopic treatment, only 14% of the patients are still free of pain.[61] In recent literature, a block of the plexus coeliacus via EUS is increasingly used for cancer pain but also for pancreatitis.

Two reviews on endoscopic US-guided plexus coeliacus neurolysis (celiac plexus neurolysis [CPN]) in pancreatic cancer as well as chronic pancreatitis patients were published recently.[62,63]

Local anesthetics alone or in combination with steroids are injected. In a few cases, alcohol was injected. These studies have had a short effect and short follow-up periods, except for the study of Gress et al.[64] Endoscopic US-guided CPN is often described as safe. Diarrhea and hypotension are minor and transient side effects. Also empyema has been described. Recently a case report of infarction of the spleen, pancreas, and gastric antrum was published.[65] An ischemic injury occurred due to diffusion of ethanol into the celiac artery with subsequent arterial vasospasm. Paraplegia, a rare but well-established adverse

side effect of CPN, is thought to be secondary to diffusion of the neuroablative alcohol into the arteries supplying the spinal cord.[3–5]

Surgery

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 are intended to reduce pain by decompression of the ductus pancreaticus. 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. Two recent randomized studies show that these surgical procedures lead to better results.[61,66] The percentage of patients who are free of pain after 5 years is 40%.

IV.B OTHER TREATMENTS

The results of the treatments discussed below (pancreatic enzyme supplementation, octreotide, and antioxidants) are not unambiguously proven in randomized studies.

Enzyme Supplementation

The assumed mechanism of action of pancreatic enzymes with respect to pain relief reflects the role they play in the negative feedback of the pancreatic exocrine function. A CCK-releasing peptide is released in the duodenum and denaturized by trypsin. In patients with chronic pancreatitis, there is a reduced release of this trypsin, a reduced breakdown of CCK-releasing peptides with increases in pancreatic enzymes and flow in the pancreatic duct resulting in pain. Oral pancreatic enzymes lead to an increased breakdown of CCK-releasing peptides.

Two old studies show that treatment with pancreatic enzymes actually does lead to pain reduction.[67,68] The best response was obtained in young women with idiopathic chronic pancreatitis without steatorrhea. Four other studies found no effect of enzyme preparation on pain. Meta-analysis of these six randomized, double-blind placebo-controlled studies did not show a relevant, significant effect of treatment with enzyme preparations.[69] Strikingly though, the two studies showing an effect of pancreatic enzymes used nonenteric-coated preparations whereas the other four studies used enteric-coated preparations.

Octreotide

Octreotide—a somatostatin-analog with a prolonged half-life, stronger action, and the option to be administered subcutaneously—has been investigated for its efficacy in chronic pancreatitis. Octreotide inhibits exocrine pancreatic function. However, these studies could not establish a significant effect on pain reduction.[46]

Antioxidants

Lower plasma levels of several antioxidants (eg, selenium, vitamin A, vitamin E, and beta carotene) have been demonstrated in patients with chronic pancreatitis. There was a lower expression of antioxidants in the pancreatic tissue of patients with chronic pancreatitis than in healthy pancreatic tissue. Lower antioxidant levels may activate oxygen radicals, which may cause metabolic changes resulting in pancreatic ischemia. Oxidative stress is one of the assumed causes of pain produced by chronic pancreatitis. Two studies achieve pain reduction with dietary supplements containing antioxidants.[46,70]

Allopurinol, which reduces the formation of oxygen radicals by inhibiting xanthineoxidase, has been investigated in a cross-over double-blind study in 13 patients with chronic pancreatitis. Allopurinol was proven to be ineffective. However, another study in which allopurinol was combined with intramuscular pethidine showed a significantly better effect compared to treatment with pethidine alone.[71,72]

IV. SUMMARY

Chronic pancreatitis is a progressive inflammatory reaction of the pancreas that causes irreversible morphological changes of the parenchyma (fibrosis, loss of acini and islets of Langerhans, and pancreatic stone formation) as well as the ductus pancreaticus (stenosis).

Pain in chronic pancreatitis requires a multidisciplinary approach, in which lifestyle changes are essential.

If the patient suffers from pseudocysts, obstruction of the ductus choledochus or the duodenum, this should be treated first.

Treatment with pancreatic enzyme supplementation, octreotide, and antioxidants can be considered, but

results have not been proven unambiguously in randomized studies.

The use of analgesic medication generally, and opioids in particular, should be accompanied by evaluation of the degree of addiction and, if indicated, close supervision.

Radiofrequency treatment of the nervi splanchnici can be considered in patients with pain that is refractory to conservative treatment.

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