Chronic Pancreatitis – Pathogenesis and Management

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This is to acknowledge that Deepak Agrawal, M.D. has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Agrawal will not be discussing off-label uses in his/her presentation.

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Particular interests

My clinical interests are related to pancreas and biliary disorders such as bile duct stones, cholangiocarcinoma, acute and chronic pancreatic disorders and pancreatic cancer. Additionally, I have an interest in therapeutic/advanced endoscopy. This involves procedures such as endoscopic ultrasound, ERCPs, luminal stent placements etc.

Purpose/Overview

The purpose of this review on chronic pancreatitis is to impress that CP is a *continuing* inflammatory process with *irreversible* changes. The main symptom in early CP is only pain and in this stage the diagnosis and treatment can be particularly challenging. Finally, I want to discuss the concept of pancreatic neuropathy to explain the severe pain that patients experience.

Objectives

- Understand the pathogenesis of CP
- Indications and limitations of different imaging modalities
- Understand pancreas function tests
- Pain management in CP

Definition of chronic pancreatitis

Chronic Pancreatitis (CP) is continuing inflammatory disease of the pancreas, characterized by irreversible morphological change, and typically causing pain and or permanent loss of function, eventually leading to malnutrition and diabetes.

This definition highlights key elements in the pathogenesis of CP. First it is a continuum rather than a distinct entity. Second, the inflammatory changes are irreversible and cause changes in morphology and compromises the function of the pancreas. Finally, pain is a dominant presentation of CP.

The word chronic is often a source of confusion since “chronic” is used in many different contexts in medicine. It may mean something temporal, for example, chronic diarrhea means diarrhea, which has been present for greater than 4 weeks. It is sometimes used to indicate persistence of infection, for example chronic hepatitis. In CP, the word chronic, strictly speaking, suggests irreversibility.

Pathogenesis

Many theories have been proposed over the last few years to explain pathogenesis of CP (1). All these theories tried to explain the pathological hallmarks of CP: inflammation, glandular atrophy, ductal changes, and fibrosis. The following hypotheses gained more acceptance: toxic-metabolic, oxidative stress, stone and duct obstruction, necrosis-fibrosis and primary duct. These theories are briefly described below (1).

Oxidative Stress Theory

It is proposed that the root cause of pancreatic disease is the over activity of hepatic mixed-function oxidases. These enzymes detoxify harmful blood-borne substances but in that process generate reactive molecules that can produce oxidative damage. The pancreas is exposed to this "oxidative stress" through the systemic circulation or through the reflux of bile into the pancreatic duct, leading to inflammation and tissue damage. This oxidative stress gets worsened by certain inducers such as alcohol. The main criticism about this theory is the chicken-and-egg phenomenon – Is the presence of oxidized products a cause or a result of pancreatic inflammation.

Toxic-Metabolic Theory

This theory suggests that changes of CP are due to direct cellular damage by alcohol. Alcohol produces cytoplasmic lipid accumulation within the acinar cells, leading to fatty degeneration, cellular necrosis, and eventual widespread fibrosis. The concept is similar to pathogenesis of alcoholic liver disease. A criticism of this theory is the lack of proof that "steatopancreatitis" is a true precursor to fibrosis, rather than a parallel, reversible, alcohol-related lesion.

Stone and Ductal Obstruction Theory

According to this theory alcohol causes CP by making the pancreatic fluid

lithogenic, leading to the formation of protein plugs and stones. Chronic contact of the stones with the ductal epithelial cells produces ulceration and scarring, resulting in obstruction, stasis, and further stone formation. Eventually, atrophy and fibrosis develop as a result of this obstructive process. This theory is attractive since calcifications and stones are more common in CP. However, protein plugs are not found in all cases of CP and particularly not in the early stages of disease. Furthermore, it has not been firmly established whether stone formation precedes or follows pancreatic fibrosis.

Necrosis-Fibrosis Hypothesis

This theory is different from other theories, in that it postulates that CP begins at the level of the pancreatic ductule rather than acinar cells. Inflammation and necrosis from episodes of acute pancreatitis produces scarring in the peri-ductular areas. This scarring leads to obstruction of the ductules, leading to stasis within the duct and secondarily, stone formation. Severe obstruction results in atrophy and fibrosis. Support for this theory comes from histopathological studies that revealed mild peri-lobular fibrosis in patients with advanced CP.

Primary Duct Hypothesis

According to this hypothesis, the primary pathogenic factor leading to duct destruction is an immunologic attack of the duct epithelium, leading to inflammation and scarring of the ductal architecture. The target of this attack may be some specific genetic or acquired antigen on the duct epithelium. In this way, CP is an autoimmune, "duct-destroying" disease, analogous to primary sclerosing cholangitis. Alcohol may initiate this sequence through some modulation of target antigens within the duct epithelium. Alcohol may also exert a directly toxic effect on the ductal epithelium, through stagnation within the lumen. Confirmation of this hypothesis is needed.

SAPE hypothesis (Sentinel Acute Pancreatitis Event)

The SAPE hypothesis incorporates many features of traditional hypotheses into a single unifying concept. According to this hypothesis, the first pancreatic insult occurs in acinar cells in response to insults such as alcohol, which up-regulate trypsin activation, in turn producing an early inflammatory response consisting of proinflammatory cells, and cytokines. At this point, removal of the inciting factor(s) results in healing. If, however, the pancreatic cytokine secretion continues, activated pancreatic stellate cells secrete collagen and set the stage for fibrosis and CP. The hypothesis is illustrated in Figure 1.

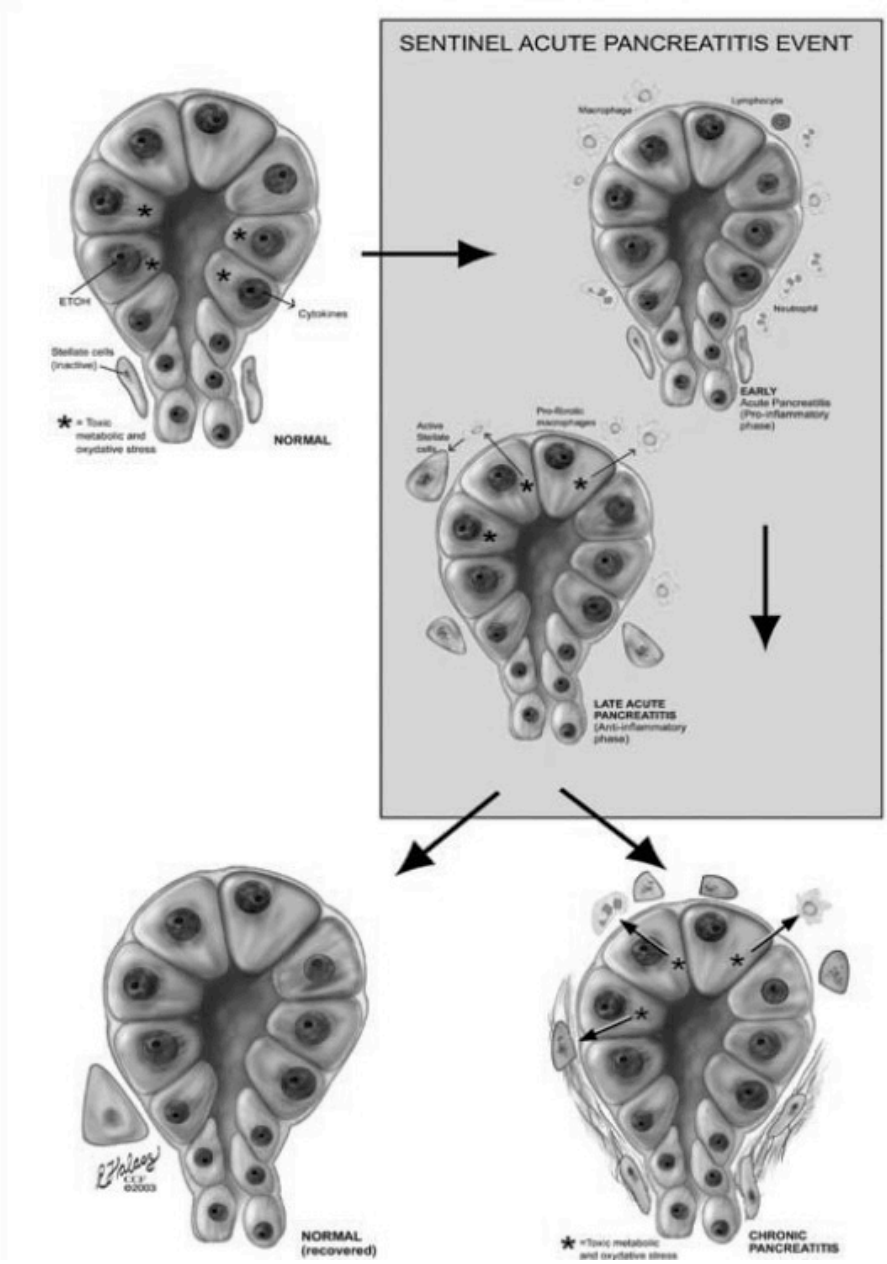


Figure 1:
SAPE hypothesis
(J Gastroenterol. 2004;99(11):2256-70)

Risk factors for Chronic Pancreatitis

Major predisposing risk factors to 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)

Toxic-metabolic	Autoimmune
Alcoholic	Isolated autoimmune CP
Tobacco smoking	Syndromic autoimmune
Hypercalcemia	CP associated with
Hyperlipidemia	-Sjögren's syndrome
Chronic renal failure	-Inflammatory bowel disease
Medications-Phenacetin abuse	-Primary biliary cirrhosis
Toxins-organotin compounds (e.g. DBTC)	Recurrent and severe acute pancreatitis
	Postnecrotic (severe acute pancreatitis)
	Recurrent acute pancreatitis
	Vascular diseases/ischemia
Idiopathic	Postirradiation
Early onset	
Late onset	Obstructive
Tropical	Pancreas divisum
	Sphincter of Oddi disorders
Genetic	(controversial)
Hereditary pancreatitis-cationic trypsinogen	Duct obstruction (e.g. tumor)
	Preampullary duodenal wall cysts
CFTR mutations	Posttraumatic pancreatic duct scars
SPINK1 mutations	

Table 1: TIGAR –O classification
Gastroenterology. 2001;120(3):682-707

We will discuss two of the more common etiologies in detail.

Alcohol: is the leading cause of CP. Although alcohol is implicated in up to 60% of CP, 95% of people who consume alcohol in excess do not develop CP. This suggests that there are other factors, possibly genetic, which predispose patients to developing CP. CP is associated with chronic, sustained use of alcohol. Reports suggest that 50-60 grams of alcohol for 10 years is necessary for alcoholic pancreatitis to develop.

Genetic: Idiopathic causes are thought to have some genetic basis, likely gene mutations, which have not been discovered so far. The three gene defects, we test for include: PRSS1, SPINK1 and CFTR, which are described below.

PRSS1, the cationic trypsinogen gene, is associated with hereditary pancreatitis. Normally, if trypsinogen becomes prematurely activated within the pancreas, it is degraded by trypsin-activated proteases. A gain-of-function mutation (autosomal dominant, 80% penetrance) in PRSS1 produces a type of trypsin, which is

resistant to degradation by proteases.

The second mutation that is normally checked for is SPINK1, which inhibits trypsinogen prematurely activated within the pancreas. SPINK1 is a loss of function mutation that is strongly associated with idiopathic disease but is thought to be a predisposing or modifying factor rather than being directly causative.

Idiopathic CP is associated with another mutation in the CFTR gene. CFTR transports bicarbonate and glutathione—which facilitate the solubility of mucins in secretions—across the luminal membrane of ductal cells adjacent to the centroacinar space. Patients can have one abnormal recessive allele, but possession of two confers a 40 times increased risk of developing idiopathic CP, which rises to 500 times in patients who also have a SPINK1 mutation.

Patients with hereditary pancreatitis have a 50-fold increase in their risk for developing pancreatic cancer, particularly if they inherit the gene from their father. Tobacco use increases the risk of pancreatic cancer in patients with hereditary pancreatitis by a factor of 150-fold and reduces the average age of onset by 20 years.

Should we order genetic testing for unexplained CP? Although genetic tests for the mutation which causes hereditary pancreatitis is readily available, a number of important issues needed to be considered before ordering genetic testing for a patient suspected of having the disease. At this time a positive genetic test has little impact on disease management and may adversely affect a patient's ability to secure insurance or employment. However the results of genetic testing may help patients better understand their disease, may be useful in family planning, and may lead to lifestyle changes (e.g., abstinence from alcohol and tobacco use) that may slow the progression of disease and reduce the risk of pancreatic cancer.

Mechanism of pain

Pain in CP is now believed to have three important components: “peripheral nociception,” “peripheral/pancreatic neuropathy and neuroplasticity,” and “central neuropathy and neuroplasticity.” It seems that CP involves sustained sensitization of pancreatic peripheral nociceptors by neurotransmitters and neurotrophic factors following neural damage. This peripheral pancreatic neuropathy leads to intrapancreatic neuroplastic alterations that involve a profound switch in the autonomic innervation of the human pancreas via “neural remodeling.” This peripheral neuropathy leads to overactivation of spinal sensory second order neurons, which in turn assume a hyper excitable state. Finally, supraspinal regions in the brainstem and cerebrum exacerbate this caudal hyper activation via descending facilitation and reorganization to process even more input from the periphery. Therefore, in the case of this neuropathic pain syndrome in CP, there is a clear domination of neuropathic pain mechanisms, which, however, in contrast with primary neuropathic syndromes, show a major dependence from the ongoing noxious stimulation from peripheral nociceptors (3). (Figure 2)

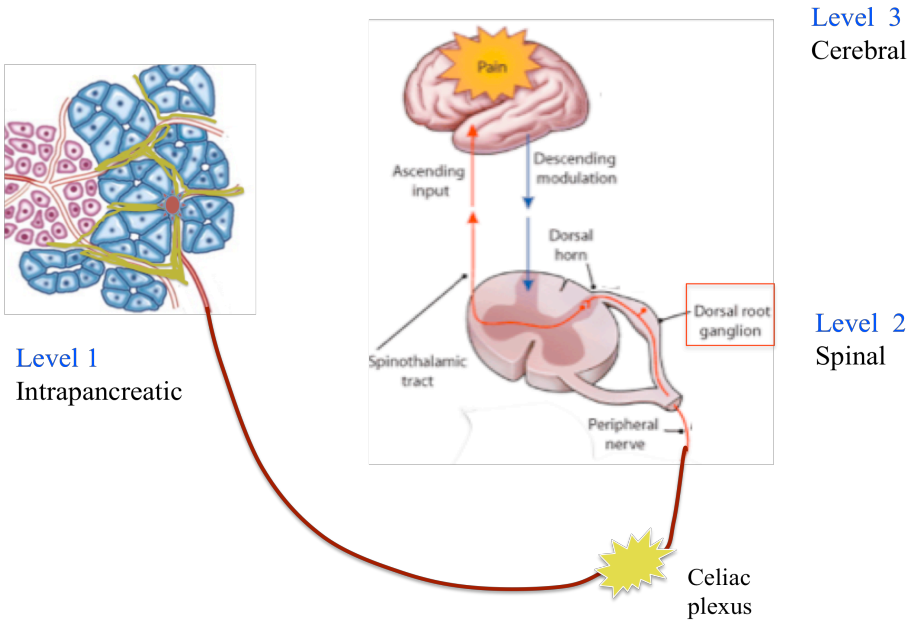


Figure 2: Multilevel neuropathic pain syndrome

Diagnosis of CP

A. Imaging
B. Pancreas Function tests

Imaging

In early stages of disease progression, results from these tests can be negative or inconclusive. In later stages, marked changes in pancreatic structure and function make diagnosis much easier and more accurate. However, late in the disease course, there is less opportunity to interrupt disease progression. Accurate diagnosis is therefore especially important during the early stages of disease, when patients present mainly with abdominal pain. In this group of patients, CP is both over diagnosed and under diagnosed. The three imaging studies commonly used are computed tomography (CT), magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasound (EUS).

CT scan: Characteristic findings CT include atrophy of the pancreas, a dilated pancreatic duct, and pancreatic calcifications. These features are pathognomonic of CP and can take 5 to 10 years or more to develop. Pancreatic calcifications seem to be much more common in patients with certain forms of CP, especially those with hereditary pancreatitis (caused by variants of PRSS1) and patients who smoke or drink alcohol. The disadvantage of CT scan is that it is not good for detecting early changes of CP such as involvement of side branches and fibrosis in the pancreatic parenchyma.

MRI/MRCP: is not increasingly being used at most institutions since MRCP allows characterization of the pancreatic ductal anatomy. The disadvantage is that it often misses calcifications. Administration of secretin during MRCP improves the quality of images of the pancreatic duct and better visualization of the side branches. However despite some early promising reports, the use of secretin MRCP is still limited since secretin is expensive and not widely available and more time is required for acquisition of images.

EUS: Endoscopic ultrasound is, at this time, the most sensitive imaging study available to diagnose early CP. This is because of its ability to visualize the side branches, fibrosis of ducts and in the parenchyma. However, some of the changes in the pancreas described on ultrasound can be non-specific, i.e. seen in old age or normal variant. Some of the changes are also subjective and interpretation is operator dependent. Consensus based criteria for EUS are now established. These are enclosed below. While it is not expected that a non-gastroenterologist know about all the criteria, it is important to realize that these just mere presence of these findings does not mean that the patient has CP and the imaging may just "suggest" CP, rather than "diagnostic" of CP (4). The changes seen on endoscopic ultrasound and their histological correlation are mentioned in Table 2 and 3. The Rosemont classification which describes probability of chronic pancreatitis based on EUS features is mentioned in Table 4.

TABLE 2. Consensus-based parenchymal features of CP

Feature	Definition	Major criteria	Minor criteria	Rank	Histologic correlation
Hyperechoic foci with shadowing	Echogenic structures ≥2 mm in length and width that shadow	Major A		1	Parenchymal-based calcifications
Lobularity	Well-circumscribed, ≥5 mm structures with enhancing rim and relatively echo-poor center			2	Unknown
A. With honeycombing	Contiguous ≥3 lobules	Major B			
B. Without honeycombing	Noncontiguous lobules		Yes		
Hyperchoic foci without shadowing	Echogenic structures foci ≥2 mm in both length and width with no shadowing		Yes	3	Unknown
Cysts	Anechoic, rounded/elliptical structures with or without septations		Yes	4	Pseudocyst
Stranding	Hyperechoic lines of ≥3 mm in length in at least 2 different directions with respect to the imaged plane		Yes	5	Unknown

Attendees ranked these features according to predictive value (1 = highest predictor) with an electronic key pad.

TABLE 3. Consensus-based ductal features of CP

Feature	Definition	Major criteria	Minor criteria	Rank	Histologic correlation
MPD calculi	Echogenic structure(s) within MPD with acoustic shadowing	Major A		1	Stones
Irregular MPD contour	Uneven or irregular outline and ectatic course		Yes	2	Unknown
Dilated side branches	3 or more tubular anechoic structures each measuring ≥1 mm in width, budding from the MPD		Yes	3	Side-branch ectasia
MPD dilation	≥3.5-mm body or >1.5-mm tail		Yes	4	MPD dilation
Hyperechoic MPD margin	Echogenic, distinct structure greater than 50% of entire MPD in the body and tail		Yes	5	Ductal fibrosis

Table 2,3: EUS findings in chronic pancreatitis

I. Consistent with CP

A. 1 major A feature (+) ≥3 minor features

B. 1 major A feature (+) major B feature

C. 2 major A features

II. Suggestive of CP†

A. 1 major A feature (+) <3 minor features

B. 1 major B feature (+) ≥3 minor features

C. ≥5 minor features (any)

III. Indeterminate for CP†

A. 3 to 4 minor features, no major features

B. major B feature alone or with <3 minor features

IV. Normal

≤2 minor‡ features, no major features

Table 4: Rosemont criteria of chronic pancreatitis

Pancreas Function tests

Pancreas has exocrine and endocrine function. The exocrine function includes secretion of digestive enzymes and bicarbonate rich juices, which help in digestion of food. Decreased exocrine function results in steatorrhea. However, pancreas has a large functional reserve and normally only 10% of the pancreas is enough to perform the digestive function. This means that steatorrhea does not develop until very advanced disease, till almost 90% of the pancreas function is lost. This makes diagnosis of early CP particularly challenging. For more than 50 years, the “gold standard” for detection of fat malabsorption had been a 72-hour quantitative stool collection measured for its fatty acid content by the titration method of van de Kamer. With this test, fecal excretion of greater than 7 g/d of fat is considered abnormal, although in the setting of diarrhea, as much as 14 g/d may be excreted by healthy persons. Patients need to maintain a high-fat (100g) diet for three days before beginning the collection of stool sample. This aspect is often overlooked in clinical practice. Moreover, performing this test is difficult logistically for centers unaccustomed to the procedure and usually abhorred by patients and laboratory technicians. This test is now largely replaced by analysis of fecal elastase 1 (FE1) concentration.

Elastase is an enzyme secreted by the pancreas and correlates well with secretion of amylase and lipase. It is not degraded during its transit in the gut and gets enriched 5-6 times, making it easier to detect. It is a cheap, easy-to-perform, indirect test of pancreatic function without prior hormonal stimulation. Fecal elastase levels <200 ug/g are highly suggestive of pancreas insufficiency. Unfortunately, FE1 has multiple diagnostic limitations. First, is the concern about falsely low levels in patients with watery diarrhea. This is important since physicians are now ordering it as part of work-up of chronic diarrhea and we are seeing falsely levels. It is to be remembered that sensitivity of FE1 in absence of history of steatorrhea is quite low (about 30%). Second, the test may not differentiate between pancreatic failure due to pancreatic parenchymal destruction, failure due to improper pancreatic stimulation after enteropathies affecting duodenal epithelium, or failures in other hormonal and neurologic stimulation of the pancreas. Thus, FE1 cannot differentiate true primary pancreatic failure from other types of pancreatic malabsorption (5).

Endoscopic pancreas function test: These tests are type of direct hormone-stimulated pancreatic function tests (PFTs), which are the most sensitive and specific tests for assessing the pancreatic exocrine reserve. They involve administration of secretin, followed by collection and analysis of the resulting pancreatic secretions. The rationale is that administration of secretin stimulates the pancreas to secrete bicarbonate and diseased pancreas (even in early stages) would not be able to respond to stimulation and thus the bicarbonate levels would be low. These tests used to be performed by passing tubes from the nose into the duodenum to collect juices. The obvious disadvantages were discomfort to patients, ineffective collection of juices and long time for the test. These tests are

now performed endoscopically and the secretions are collected for a shorter time. A commonly accepted protocol is described below.

Procedure: Endoscopy is performed in standard fashion. Twenty-five minutes after secretin injection, an upper endoscopy is performed. Thirty minutes after secretin injection, the tip of the endoscope is placed distal to the papilla and duodenal juice collected in 3 separate samples at 35, 40, and 45 minutes after secretin injection. Each sample is collected for 5 minutes using standard fluid collection traps. The pH and amount of each sample was measured. Duodenal juice with pH less than 6 is discarded because of possible pollution from gastric juice. The samples are then sent to lab for bicarbonate analysis. The peak value of bicarbonate among the 3 samples less than 80 mM/L is considered diagnostic for pancreatic exocrine insufficiency (6).

Limitations of endoscopic PFTs: Endoscopic methods have simplified direct PFTs, and made them more accessible to clinicians and patients. However, there are acknowledged limitations. First, even when shortened protocols are used, the ePFT remains a time-consuming test, requiring 30-45 min of prolonged endoscopy. Second, the inability to accurately quantify fluid volume prevents calculation of enzyme output, arguably the optimal measure of acinar capacity. Finally, although intravenous sedation in low doses does not appear to substantially affect exocrine secretion, the effect of higher levels of sedation, as required for many patients with CP, has not been adequately studied.

Management of CP

Management of CP consists of 1. Management of pain 2. Management of exocrine insufficiency.

Management of pain

1. Medical
   - Cessation of alcohol and tobacco
   - Non-steroidal anti-inflammatory drugs
   - Non-opioids – Tramadol, Pregabalin, Antioxidants, Pancreatic enzymes
   - Opioids

2. Endoscopic (for large duct disease)
   - Sphincterotomy
   - Pancreatic duct stent placement
   - Removal of stones from pancreatic duct
   - Celiac plexus block

3. Surgical

Non-opioid pharmacological management of pain

Tramadol is commonly used for this purpose in dosages of 200 to 400 mg daily, although higher dosages are given to some patients. Some consider it an opioid since it acts on mu receptors but more apt classification is atypical centrally acting analgesic.

Pregabalin: Many other centrally acting agents have been tried. These include tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and gabapentoids. Of these, only pregabalin has been studied in a randomized controlled trial in patients with chronic pancreatitis (7). Patients treated with pregabalin (up to 300 mg twice daily) had reduced pain compared with those given placebo and were able to reduce opioid use. Side effects were more common in the pregabalin group (lightheadedness or a feeling of being drunk). Preliminary studies suggest that pregabalin inhibits central sensitization. It is not clear whether other adjunct agents are equally effective or if combinations of these agents are more effective.

Antioxidant therapy: CP patients have a decreased micronutrient intake (Vitamin E, riboflavin, choline, magnesium, copper, manganese and sulphur). This is due to diet modifications due to pain, as well as to a lower caloric intake. This points to the possibility that micronutrients deficiency may contribute to increased oxidative stress. Activation of oxygen free radicals can cause metabolic changes leading to pancreatic ischemia (8).

There have been multiple small studies but they had small number of patients, different etiologies of pancreatitis, different anti-oxidant preparations and different duration of treatment. A recent double-blind, randomized, controlled trial comparing antioxidant therapy (Antox version 1.2) with placebo showed no difference between the two groups. Despite, lack of data supporting the use of antioxidants many physicians still use it since the treatment is considered non-toxic and safe.

Pancreatic enzymes: The presumed mechanism for pain relief after the administration of oral pancreatic enzymes is thought to involve the negative feedback inhibition to the pancreas. A cholecystokinin (CCK)-releasing peptide in the duodenum is normally denatured by pancreatic trypsin. In CP, damage to acinar cells results in decreased secretion of pancreatic trypsin and consequently insufficient denaturing of the CCK-releasing peptide. This then leads to the potentiation and increased release of CCK, which causes pancreatic pain related to an increase in pancreatic enzyme output. When pancreatic enzymes are administered orally, there is more complete denaturing of the CCK-releasing peptide, thereby diminishing the release of CCK (9,10)

It is believed that non-enteric coated enzymes are preferred for control of pain since they are more likely to be active in the duodenum and thus decrease release of CCK. Studies have yielded conflicting results, and a meta-analysis did not demonstrate a benefit (9). However, this metanalysis combined studies that used

enteric and non-enteric coated enzymes. So, it's difficult to generalize the results. Many physicians still prescribe pancreatic enzymes, given the absence of significant risk.

Endoscopic treatment of CP

The goals of endoscopic therapy are to relieve pain and improve pancreatic duct drainage. The rationale of endoscopic treatment is that pain in CP is a result of high intraductal pressure and by placing a stent or cutting the pancreatic sphincter, the pressure can be relieved.

Patients with pancreatic duct strictures can be treated with dilation of the stricture and placement of a stent. Stents can be successfully placed 95% to 100% of the time with initial improvement in pain in 74% to 94% of patients and a complication rate of 16%. However, over long term, this approach is generally not successful, and most of these patients will require surgery to treat the problem (11,12).

Pancreatic duct stones can be removed by endoscopic means with or without the use of extracorporeal shock wave lithotripsy. Stone clearance is achieved in about 80% to 85% of patients, with initial pain relief in about 90%. However, long-term pain relief is seen in only 50% to 70%; and a substantial number of patients will eventually require an operation.

Patients with CP and small ducts may have sphincter of Oddi dysfunction as the cause and frequently benefit from endoscopic sphincterotomy of the pancreatic duct with short-term postprocedure stenting. This can be done with a complication rate of about 5%.

Endoscopic celiac plexus block

Celiac plexus block (CPB) may be administered via endoscopic or interventional radiological means. Endoscopic route offers a few advantages: 1. It is easier to perform. 2. Pain relief after endoscopic ultrasonography-guided celiac plexus block seemed to persist longer that CT-guided block. 3. A rare but dreaded complication of paraplegia has not been described after endoscopic route, probably because of the anterior transgastric approach taken during endoscopic ultrasonography.

Although CPB is widely used, there have been relatively few formally reported experiences with nerve blocks for long-term therapy of CP. Because of possible concerns about potential irreversible nerve injury, injection of steroids for the treatment of CP has been recommended, instead of the use of alcohol injected into the celiac plexus (principally used in the treatment of cancer pain).

CPB benefits about 50% patients and the benefit persists only 12-24 weeks. Younger patients (< 45 years) and patients with previous pancreatic surgery for CP do not appear to benefit from the block.

Surgical treatment for CP

Drainage procedures: More than 90% of patients undergoing operations have pain as a major symptom. The goals of surgery are to relieve pain, restore flow through obstructed channels, preserve pancreatic parenchyma, improve nutrition, prevent recurrent hospitalization, and, if possible, prevent or delay further functional derangements. For patients with large pancreatic ducts (> 7 mm), a lateral pancreaticojejunostomy (modified Peustow procedure) is the procedure of choice and produces pain relief in up to 75% of patients with morbidity of 9% to 21% and low mortality. For patients with small ducts, an analogous operation has been described in which a lateral V-shaped incision is made into the gland and the pancreas is drained through a lateral pancreaticojejunostomy.

Resection procedures: For patients with CP and an inflammatory mass in the head of the gland, a lateral pancreaticojejunostomy with extended drainage (Frey procedure) can be performed with pain relief in up to 75% patients.

Pancreatic resections for CP include the standard pancreaticoduodenectomy (Whipple procedure) with or without preservation of the pylorus and a duodenum-sparing pancreatic head resection. Because substantial amounts of pancreatic tissue are resected, the likelihood of development of either exocrine or endocrine insufficiency is greater. These procedures should be reserved for those patients who have failed a previous lateral pancreaticojejunostomy or those who have chronic pain and either a dominant mass in the head of the pancreas or nondilated pancreatic ducts.

Denervation procedures: Most of the sensory nerves returning from the pancreas pass through the celiac ganglion and splanchnic nerves. It is hypothesized that interruption of these fibers may lessen pain. The studies on splanchnicectomy are small and await confirmation. This treatment has not been widely accepted. Of note, pancreaticoduodenectomy and duodenum-preserving resection of the pancreatic head may well confer pain relief at least in part through denervation.

Treatment of exocrine pancreatic insufficiency (EPI)

Management approaches to (EPI) include the following:

- Lifestyle modifications (limitation of alcohol intake, cessation of smoking, and consumption of a well-balanced diet)
- Vitamin supplementation (primarily the fat-soluble vitamins A, D, E, and K)
- Pancreatic enzyme replacement therapy (PERT), which is the therapeutic mainstay

PERT is the basis of treatment of EPI ; the endpoints of treatment are normalization of gut absorption and correction of nutritional deficiencies. The typical indications for initiating PERT are progressive weight loss and steatorrhea.

The pancreatic enzyme products are extracts of porcine pancreas that contain all 3 pancreatic enzymes (i.e., amylase, protease, and lipase) in varying proportions.

However, it is lipase that plays the paramount role in therapy. The following 6 pancreatic enzyme products (PEPs) have been approved by the US Food and Drug Administration (FDA):

Drug	Active ingredients	Time of FDA approval	Strength (amylase, lipase, and protease)
Creon®	Capsule, delayed release; oral	2009	30,000 USP U; 6000 USP U; 19,000 USP U 60,000 USP U; 12,000 USP U; 38,000 USP U 120,000 USP U; 24,000 USP U; 76,000 USP U
Zenpep®	Capsule, delayed release, oral	2009	27,000 USP U; 5000 USP U; 17,000 USP U 55,000 USP U; 10,000 USP U; 34,000 USP U 82,000 USP U; 15,000 USP U; 51,000 USP 109,000 USP U; 20,000 USP U; 68,000 USP U
Pancreaze®	Capsule, delayed release, oral	2010	17,500 USP U; 4200 USP U; 10,000 USP U 43,750 USP U; 10,500 USP U; 25,000 USP U 61,000 USP U; 21,000 USP U; 37,000 USP U 70,000 USP U; 16,800 USP U; 40,000 USP U
Ultresa®	Capsule, delayed release, oral	2012	27,600 USP U; 13,800 USP U; 27,600 USP U 41,400 USP U; 20,700 USP U; 41,400 USP U 46,000 USP U; 23,000 USP U; 46,000 USP U
Viokace®	Tablet, oral	2012	39,150 USP U; 10,440 USP U; 39,150 USP U 78,300 USP U; 28,880 USP U; 78,300 USP U

Abbreviations: FDA, Food and Drug Administration; USP U, United States Pharmacopeia units.

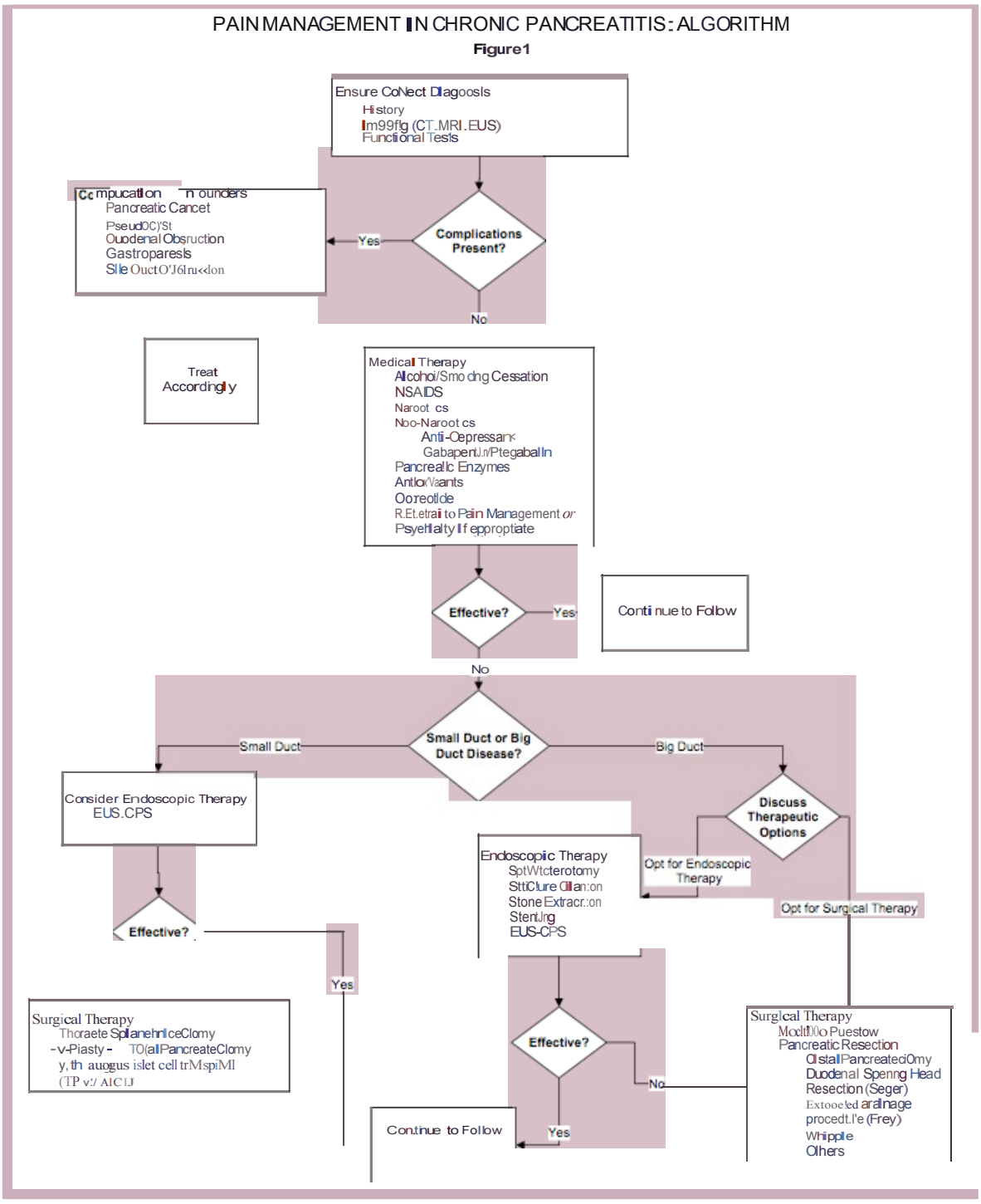
These PEPs are not interchangeable. For example, Viokace, unlike the other 5 products, lacks an enteric coating and must be taken with a proton pump inhibitor.

Because exogenous pancreatic enzymes should exert their action on the ingested meal and because gastric emptying of nutrients should occur in parallel with pancreatic enzymes reaching the duodenum, PEPs are administered together with meals and snacks. When a sufficient enzyme concentration is delivered into the duodenal lumen simultaneously with a meal, fat absorption is enhanced.

PEP dosing for PERT is based on the content of lipase units. The pancreatic lipase replacement dose should be adjusted on the basis of body weight, clinical symptoms, and stool fat content. Several days should be allowed between dose adjustments. An approximate starting dose is about 50-60,000 USP lipase. The dose may be increased to 90,000 USP depending on the response (assessed by improvement in diarrhea and sometimes dyspeptic symptoms)

PAIN MANAGEMENT IN CHRONIC PANCREATITIS: ALGORITHM

Figure1



References

1. Stevens T, Conwell DL, Zuccaro G. Pathogenesis of chronic pancreatitis: an evidence-based review of past theories and recent developments. Am J Gastroenterol. 2004;99(11):2256-70.
2. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology. 2001;120(3):682-707.
3. Demir IE, Tieftrunk E, Maak M, et al. Pain mechanisms in chronic pancreatitis: of a master and his fire. Langenbecks Arch Surg. 2011;396(2):151-60
4. Catalano MF, Sahai A, Levy M, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. Gastrointest Endosc. 2009;69(7):1251-61.
5. Fine KD, Ogunji F. A new method of quantitative fecal fat microscopy and its correlation with chemically measured fecal fat output. Am J Clin Pathol. 2000;113(4):528-34.
6. Erchinger F, Engjom T, Tjora E, et al. Quantification of pancreatic function using a clinically feasible short endoscopic secretin test. Pancreas. 2013;42(7):1101-6
7. Olesen SS, Bouwense SA, Wilder-Smith OH, et al. Pregabalin reduces pain in patients with chronic pancreatitis in a randomized, controlled trial. Gastroenterology 2011;141:536–543.
8. Siriwardena AK, Mason JM, Sheen AJ, Makin AJ, Shah NS. Antioxidant therapy does not reduce pain in patients with chronic pancreatitis: the ANTICIPATE study. Gastroenterology. 2012 Sep;143(3):655-63.
9. Brown A, Hughes M, Tenner S, Banks PA. Does pancreatic enzyme supplementation reduce pain in patients with chronic pancreatitis: a meta-analysis. Am J Gastroenterol. 1997;92:2032–2035.
10. Nakajima K, Oshida H, Muneyuki T, Kakei M. Pancrelipase: an evidence-based review of its use for treating pancreatic exocrine insufficiency. Core Evid. 2012;7:77-91.
11. Forsmark CE. Management of chronic pancreatitis. Gastroenterology. 2013;144(6):1282-91.e3.
12. Forsmark CE, Liddle RA. The challenging task of treating painful chronic pancreatitis. Gastroenterology 2012;143:533–535.
13. www.medscape.org