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Chronic pancreatitis, a comprehensive review and update. Part II: Diagnosis, complications, and management

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Introduction

Advances in research regarding chronic pancreatitis (CP) have improved our understanding of this disease. Despite this progress, the management of CP still remains less than optimal, with many patients who are symptomatic and have poor quality of life.

Optimal management begins with an accurate diagnosis, identifying the cause, assessing the reversibility of the cause, and then the evaluation followed by treatment of symptoms and complications. This review focuses on areas with updated recent evidence.

Diagnosis of CP

Accurate diagnosis of CP is often challenging especially in early stages of the disease where patients lack classical clinical evidence of CP.

Chronic pancreatitis is usually diagnosed with historical clinical information and with the results of radiographic studies and laboratory tests of pancreatic function.

Numerous diagnostic tests have been developed. The sensitivity and specificity of many of these tests are either poor or unknown, and some older tests such as bentiromide test, dual Schillings test, and olein absorption are not commonly utilized in current clinical practice.

Is histologic fibrosis the gold standard to diagnose chronic pancreatitis?

Histologic evidence of fibrosis and parenchymal atrophy is the most specific diagnostic finding; however, it is rarely available.

In addition, pancreatic fibrosis without inflammation or parenchymal destruction may be seen in asymptomatic individuals. This “bland fibrosis,” which is found associated with alcoholism, smoking, and ageing, should be distinguished from chronic pancreatitis. While this

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bland fibrosis is clinically silent, radiologic appearances may be indistinguishable from symptomatic individuals. It is still unclear if extensive fibrosis associated with chronic alcohol use can result in functional pancreatitic insufficiency.[1]

Fibrosis and atrophy in isolation do not indicate inflammation and may be the result of normal "aging" of the pancreas. Therefore, utmost caution should be used in diagnosing chronic pancreatitis based on endoscopic ultrasound (EUS) findings alone in the absence of an appropriate clinical presentation.

Pancreatic fibrosis without pancreatitis

1. Old age
2. Smoking
3. Alcohol use

Biochemical tests

Routine lab tests are not usually helpful in diagnosing CP. Lab tests might reflect the secondary effects of chronic pancreatitis such as anemia from malabsorption, fat-soluble vitamin deficiency (low 25-hydroxy vitamin D levels and low calcium levels), and occasional elevation of alkaline phosphatase secondary to biliary compression from fibrosis-related CP.

Specific biochemical tests are less useful than imaging in diagnosing CP, although there is some evidence that these functional tests can diagnosis CP at earlier stages than imaging studies (Table 1).

Serum amylase and lipase

In contrast to acute pancreatitis, measurement of amylase and lipase are not very useful in the evaluation of CP. Amylase and lipase may be elevated, normal, or low in CP. In acute exacerbations of CP, these enzymes might be elevated; however, serum concentrations seldom reach the threshold level seen in acute pancreatitis. A very high level of amylase in a classical chronic pancreatitis patient presenting with acute abdominal pain should prompt the physician to consider evaluation for other abdominal process such as bowel perforation or obstruction.[2]

Serum trypsin

Low levels (< 20 mg/dL) of serum trypsin (a.k.a., trypsinogen) are seen in patients with advanced chronic pancreatitis who have steatorrohea.[3] Levels from 20 to 29 mg/dL are indeterminant, but sometimes represent early CP.[4] While low concentrations (< 20 mg/dL)

Table 1
Pancreatic function testing.

Enzyme assay
1. Serum trypsin
Hormone stimulation tests
1. Secretin
2. Cholecystokinin
3. Combined secretin–CCK test
Stool testing
1. 72-hr quantitative fecal fat
2. Fecal elastase
3. Fecal chymotrypsin

of serum trypsin are relatively specific for advanced chronic pancreatitis, they are not sensitive enough to be helpful in most patients with mild to moderate disease. This test is not reliable in patients who do not have steatorrhea, and low levels may be seen in other conditions associated with pancreatic ductal obstruction such as malignancy.

Another application of this test stems from the finding that trypsin levels over 150 ng/mL are indicative of pancreatic inflammation, and trypsin may be elevated even when amylase and lipase levels are normal.[3] Trypsin is usually measured using radio-immuno assay, and it takes several days to obtain results thus it is not useful in acute settings.

Stimulation tests

As the basal rate of pancreatic secretion is highly variable, the idea of supraphysiologic stimulation of the pancreas to collect and quantitate the quality of pancreatic secretions has been adopted since the 1940s.[5,6]

Secretin stimulation test

Initially publicized by Dreiling and Hollander[7] in 1948, this test involves administration of a supraphysiologic dose of secretin to produce maximal pancreatic stimulation. Pancreatic juice is collected with a Dreiling tube or an endoscope and analyzed for bicarbonate concentration. Currently, Human secretin (ChiRhoStim®) injection is available as a lyophilized powder for intravenous use in 16- and 40-mcg vials. A dose of 0.2 mcg/kg body weight by intravenous injection is administered over 1 min, and then bicarbonate levels are measured to assess the exocrine pancreas dysfunction.

How to perform secretin stimulation test

Gastro-duodenal (Dreiling) tube collection method (DT)

Following a 12-hr fast, a radiopaque, double-lumen tube is passed through the mouth, and under fluoroscopic guidance, the opening of the proximal lumen of the tube is placed in the gastric antrum and the opening of the distal lumen, just beyond the ampulla of Vater. The positioning of the tube must be confirmed and the tube secured. Intermittent negative pressure of 25–40 mmHg is applied to both lumens and maintained throughout the test. When duodenal contents have a pH of >6, a baseline sample of duodenal fluids is collected for a 10-min period.

After testing for allergies using a small test dose of Human secretin injection 0.2 mcg, Human secretin at a dose of 0.2 mcg/kg of body weight is injected intravenously over 1 min. Duodenal fluid is collected for 60 min thereafter. The sample of duodenal fluid is subsequently analyzed for volume and bicarbonate concentration. Exocrine pancreas dysfunction associated with chronic pancreatitis is indicated if the peak bicarbonate concentration for any sample is <80 mEq/L.[8]

Because of its invasive, lengthy, and cumbersome nature, this test is available only at a few specialized centers.

In the last few years, a simplified version of the secretin test has been developed. In this endoscopy-based PFT (ePFT) pioneered by Dr. Conwell's group at the Cleveland Clinic, duodenal fluid is collected under direct vision using an endoscope, and an auto-analyzer is used to measure bicarbonate concentration.

Endoscopic collection method: Endoscopic pancreatic function test (ePFT)

After testing for allergies as mentioned above, Human secretin at a dose of 0.2 mcg/kg of body weight is injected intravenously over 1 min, and an upper endoscopy is performed.

All gastric fluid is aspirated through the endoscope and discarded. After small bowel intubation to the junction of the second and third portions of the duodenum, 3–5 mL of duodenal fluid is aspirated every 15 min for an hour, and the sample of duodenal fluid is analyzed for volume and bicarbonate concentration.

Exocrine pancreas dysfunction associated with chronic pancreatitis is indicated if the peak bicarbonate concentration for any sample is < 80 mEq/L.

Stevens et al.[9] noted that the accuracy between the ePFT is similar to DT, and there is excellent correlation between peak bicarbonate levels.

Cholecystokinin (CCK) stimulation testing.

It is similar to SST; however, the CCK test is more cumbersome with marker perfusion and back titration techniques for aspiration of duodenal fluid required.

Cholecystokinin (previously called *pancreozymin*) is used to stimulate the pancreatic secretion.[10] A Japanese study noted no differences between the SST and the CCK stimulation tests.[11] Interestingly, Conwell et al. measured the lipase concentration in duodenal fluid after CCK stimulation and demonstrated that it is markedly reduced in patients with chronic pancreatitis. Peak lipase concentration is a significant predictor of chronic pancreatitis and correlates with the severity of pancreatic disease. It was suggested that the measurement of enzyme concentration instead of output could lead to the development of an endoscopic or through-the-scope screening method for assessing patients with suspected chronic pancreatitis.[12]

Is combined secretin and CCK testing better than secretin alone?

To see if combining secretin and cholecystokinin stimulation during endoscopic pancreatic function testing is better than using standard secretin alone, Stevens et al. studied 69 patients with CP and concluded that the addition of CCK does not enhance the diagnosis of CP.[13]

Should we use ePFT stimulation testing routinely to diagnose CP?

ePFT tests are currently available only in specialized centers. While the greatest sensitivity can be obtained in prolonged infusions of secretagogue to uncover a decreased pancreatic exocrine reserve, it is impractical for general clinical use.

In its current form, the ePFT requires fluid collection for 60 min, sedation, and involves significant nurse and physician effort because the endoscope remains in the duodenum for the duration of the procedure. The sensitivity and specificity of stimulation testing is 67% and 90%, respectively. With such test characteristics, an abnormal ePFT (especially mild abnormality) in a population of dyspeptic subjects with low likelihood of having chronic pancreatitis is likely to be false positive (in up to 10% of patients). Mild chronic pancreatitis with normal imaging findings on CT and MRI is often termed "minimal change CP."[14] In patients with no CT/MRI evidence of CP, and EUS findings indeterminate with a score of 4–5 (> 6 is diagnostic of small duct disease and ≤ 3 is normal pancreas),[15] ePFT could be used to assess the 60-min HCO_3 level to diagnose minimal change chronic pancreatitis.

Due to its high negative predictive value, this test may have particular value in excluding "minimal change CP."[14]

ePFT secretin stimulation testing (peak pancreas fluid $HCO_3 < 80$ meq/L) is more useful in diagnosing minimal change CP where

- CT/MRI are normal and
- EUS score is 4–5

Fecal tests

Steatorrhea occurs only when > 90% of pancreatic exocrine function is lost.

72-hr fecal fat quantitative test

The 72-hr fecal fat collection was once a routine part of the workup for malabsorption, and it still remains the gold standard for diagnosis of exocrine pancreatic insufficiency with fat maldigestion. Despite that, this test has several disadvantages limiting its clinical applicability. Patients must follow a standard diet containing 80–120 g of fat daily for 5 consecutive days, and then collect all stools over the last 3 days of the diet, which limits patient compliance. Fecal fat exceeding 7 g/day may be suggestive of PEI. However, this test is non-specific for pancreatic disease, as bacterial overgrowth, short bowel syndrome, and small bowel mucosal disease (e.g., celiac disease and Crohn's disease) could all lead to fat malabsorption resulting in steatorrhea.[16]

Fecal elastase

Due to the cumbersome nature of the 72-hr fecal fat test, measurement of fecal elastase is the preferred fecal test when evaluating pancreatic exocrine dysfunction. Elastase-1 is a specific protease from the pancreatic acinar cell that is stable in stool and correlates fairly well with ePFTs.[17] Among pancreatic function tests, fecal elastase measurement is the most sensitive and specific. Fecal elastase is tested by an ELISA technique that uses monoclonal antibodies against human pancreatic elastase and is unaffected by pancreatic enzyme replacement therapy (PERT). Low levels in the stool (< 200 g/g of stool) are suggestive of PEI.

Fecal elastase has a superior diagnostic accuracy when compared to fecal chymotrypsin (92% vs 82%), and results are reliable even 7 days post collection.[18] This test gained popularity in cystic fibrosis clinics to screen infants who may need PERT.[19]

In a recent Italian study, it was observed that fecal elastase is not a useful biomarker to assess for steatorrhea in patients with prior pancreatic resection, while low levels correlate with PEI in non-operated patients with pancreatitis.[20]

Although fecal elastase seems to be an easy non-invasive way to diagnose PEI, it may not be reliable in mild to moderate CP. However, its sensitivity in severe chronic pancreatitis is very high, reaching values close to 100%.[21,22] A recent Norwegian study demonstrated that a modified short secretin-stimulated ePFT (15-min testing) is superior to fecal elastase and more useful in diagnosing early/mild CP.[23]

Fecal chymotrypsin

The sensitivity and accuracy of fecal chymotrypsin is relatively lower than that of fecal elastase.[18] In contrast to elastase, chymotrypsin assay is affected by pancreatic enzyme intake, and therefore, patients must be off any exogenous pancreatic enzymes for at least 2 days prior to the test. Levels < 3 U/g stool are suggestive of PEI. Fecal chymotrypsin assay is not widely used in clinical practice in evaluating PEI.

Imaging tests

Plain abdominal x-ray

Pancreatic calcifications are a common finding in chronic calcific pancreatitis and are considered pathognomonic for alcoholic chronic pancreatitis in Western countries and tropical fibro-calculous pancreatitis in Asia. Calcification primarily represents intraductal calculi, either in the main pancreatic duct or in the smaller side-branch pancreatic ducts. The demonstration of speckled calcification which could be focal or diffuse along the pancreas, crossing the midline on

a plain film of the abdomen is diagnostic of chronic pancreatitis. Although the sensitivity of this finding is limited (around 30–40%), a plain film of the abdomen should be the first diagnostic test used when attempting to evaluate chronic abdominal pain as a positive finding obviates the need for additional testing.[2]

Ultrasonography

Ultrasonography has limited ability to image the pancreas, but due to its low cost and absence of ionizing radiation, this can be useful as part of initial evaluation.[24] Some of the findings that correlate well with ERCP include main pancreatic duct dilation greater than 4 mm, large cavities, and calcifications.[25]

CT scan

In current practice, CT scan abdomen is often the initial investigation when chronic pancreatitis is suspected. The sensitivity of CT scan ranges from 75% to 80% for advanced CP with calcifications, atrophy, fat replacement, cystic lesions, and ductal dilation. However, the overall sensitivity for all types of CP is 47%, with a specificity of 90%.[26,27] CT is the most sensitive and specific modality for depicting pancreatic calcifications, which may be tiny and punctate or larger and coarse.

Are pancreatic calcifications specific for the diagnosis of chronic pancreatitis?

Calcifications are thought to be pathognomonic for chronic pancreatitis and may take more than 10 years to develop. The median time to calcification is 13.1 years for alcoholic chronic pancreatitis, 16.9 years for late-onset idiopathic chronic pancreatitis, and 24.9 years for early-onset idiopathic chronic pancreatitis.[29] Pancreatic calcifications are more common in patients with certain forms of chronic pancreatitis, such as tropical pancreatitis, hereditary pancreatitis (PRSS1 variant), and alcohol- and smoking-related pancreatitis (Fig. 1).

Campisi et al.[30] reported a study of 103 patients who had pancreatic calcifications on CT scan where 68% had chronic pancreatitis, while the remaining 32% had other pancreatic diseases, including neuroendocrine tumor (13.6%), intraductal papillary mucinous neoplasm (IPMN) (4.8%), malignant IPMN (5.8%), serous cystadenoma (3.9%), and pancreatic adenocarcinoma (PCa) (3.9%).

Therefore, pancreatic calcifications do not always indicate chronic pancreatitis. Incorrect diagnosis of chronic pancreatitis in patients with pancreatic calcifications could lead to

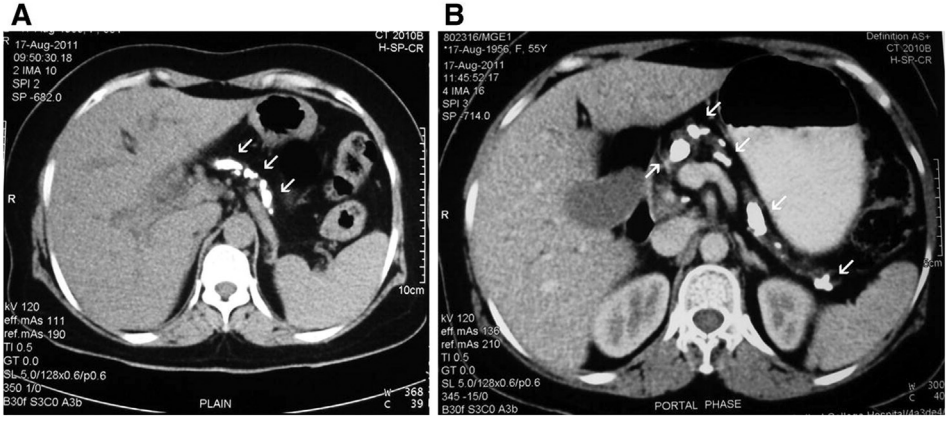

Fig. 1. Tropical calcific pancreatitis with multiple, large calculi in the dilated pancreatic duct with gross atrophy of the pancreas seen in CT scan abdomen. (Adapted with permission from Subhash et al.[28])

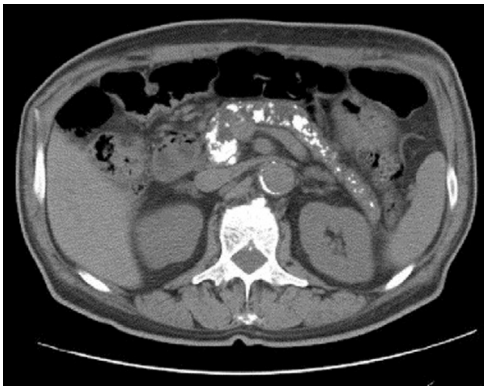

Fig. 2. Non-contrast CT scan showing extensive pancreatic calcification in a patient with a IPMN in the head of the pancreas. ERCP showed dilated pancreatic duct with mucin pouring out of the ampulla. (Adapted with permission from Zapiach et al.[31])

inappropriate treatment, such as sphincterotomy, pancreatic duct stenting, and extracorporeal shock wave lithotripsy.

In a study of 10 IPMN patients with calcifications within the pancreatic main duct or side branches, who underwent pancreatic resection, 7 were found to have adenoma, and 1 was an invasive cancer. Such calcifications in IPMN are likely due to an unrecognized form of calcifying obstructive pancreatitis, caused by prolonged obstruction of the pancreatic duct[31] (Fig. 2).

Stones are formed within pancreatic ducts and not within the parenchyma.[32] It is believed that partial obstruction of pancreatic ducts and stasis of pancreatic secretions during chronic pancreatitis favors pancreatic calculus formation. It is likely that "parenchymal"-appearing stones initially formed within small side duct branches.[30]

The specificity of pancreatic calcifications for chronic pancreatitis depends upon the intrapancreatic distribution: parenchymal 67%, intraductal 88% (present only in chronic pancreatitis and IPMN), diffuse parenchymal 91%, and coexisting intraductal and parenchymal calcifications 100%.[30] These results highlight that (main duct) IPMNs may share many chronic pancreatitis features, and distinction between chronic pancreatitis and IPMN may be a difficult task. Age-related non-specific pancreatic calcification, cystic neoplasms, and splenic artery calcification are other common mimics.[33]

Other CT findings

Pancreatic pseudocysts and other complications of chronic pancreatitis, including infection, hemorrhage with pseudoaneurysm formation, rupture with fistula formation, and gastrointestinal or biliary obstruction, are well depicted on CT.[34] Pancreatic carcinoma developing in the setting of chronic pancreatitis may be difficult to identify. Pseudotumoral enlargement around focal pancreatitis with extensive fibrous tissue proliferation usually fails to enhance after the administration of IV contrast. Obliteration of the fat sleeve around the superior mesenteric artery has been described in both chronic pancreatitis and pancreatic carcinoma.

50% of early CP patients may have a normal CT scan

MRCP

Pancreatic MRI examination consists of an abdominal MR pancreas protocol involving different phases such as T2-weighted (T2-W), T1-W, and dynamic post-contrast images in late arterial, porto-venous, and equilibrium phases. For MRCP, several 2- and 3-dimensional, heavily

T2-W images are acquired along the plane of the pancreatic duct and through the pancreas from which maximum-intensity projection images are reconstructed. In patients with moderate chronic pancreatitis, the pancreatic parenchyma shows abnormal high signal intensity on T2-W images and low signal intensity on T1-W images with delayed enhancement pattern after gadolinium administration.[35] The sensitivity of MRI is 75% for advanced disease but is as low as 25% for small duct disease or minimal change CP.[36] Clear visualization of normal or minimally dilated pancreatic ducts by MRCP is more challenging because of their small size.[37] Secretin-enhanced MRI has been shown to improve the yield in such cases.[37,38]

MRI will miss calcifications in the pancreas.

Secretin-enhanced MRCP (S-MRCP)

Duodenal filling following S-MRCP is significantly reduced in CP patients with exocrine pancreatic insufficiency compared with healthy subjects.[38] Pancreatic flow dynamics can be monitored after intravenous secretin administration, and measurement of the subsequent filling of the duodenum during MRCP can be used to evaluate the exocrine pancreatic function. Human secretin administration (intravenous) has been show to significantly improve yield of MRCP in diagnosing CP and PEI.[39,40] S-MRCP is a relatively non-invasive procedure, and approximately 5% of patients may have nausea, flushing, abdominal pain, and vomiting following secretin injection.

Secretin administration stimulates fluid and bicarbonate secretion by the pancreas, thereby improving pancreatic duct and side branch (Fig. 3). Side-branch ectasia, mild ductal dilatation with loss of the normal gentle taper, and mural irregularities are the pathognomonic MRCP features of early-stage chronic pancreatitis.[38]

For S-MRCP, 2-dimensional MR is repeated every 30 s for 10 min after intravenous administration of 0.2 mcg/kg body weight of Human secretin. Pre- and post-secretin images are then compared for changes in main pancreatic ductal caliber (compliance), better visualization of ducts and side branches, sphincter of Oddi function, and the duodenal filling. Secretin administration also increases the parenchymal signal intensity on T2-W images.

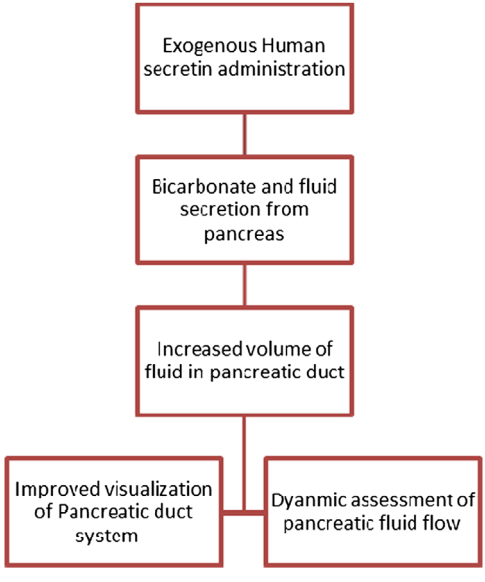

Fig. 3. Physiology of secretin MRI.

Ductal changes with secretin MRI

Secretin creates more physiologic ductal distension on T2 images.

Normal	CP
• MPD is <3 mm, and tapers smoothly to the tail • Distends about 66% in response to secretin • Returns to baseline in 10 min	• Baseline dilation, irregularity, and loss of tapering of MPD • Due to decreased pancreatic secretion and fibrosis, there in less distension of the PD • Side-branch dilation can be visualized and assessed by Cambridge classification (see below)

Parenchymal changes with secretin MRI

In CP, the glandular tissue is gradually replaced by fibrous tissue and so, decreased parenchymal signal is associated with loss of pancreatic acinar tissue.

Volume changes with secretin MRI

As mentioned above, secretin stimulates the emptying of watery bicarbonate-rich fluid in the duodenum. In normal individuals, fluid appears rapidly in the peri-ampullary duodenum, then fills and distends the duodenal bulb, and then progresses past the genu. However, in CP patients, there is a delay in filling and entry into the duodenum and decreased distension of the duodenum.[41]

Secretin-MRCP to optimally select patients for pancreatic endotherapy?

Secretin MRI is overly sensitive and may give false-positive result, particularly following episodes of acute pancreatitis. Testoni et al.[42] noted that abnormalities can be seen in asymptomatic patients with chronic enzyme elevations. However, several studies indicate that S-MRCP when combined with MRI of the pancreas enhances the diagnostic sensitivity in early chronic pancreatitis.[43] A recent study by Sherman et al.[44] found that S-MRI in comparison to MRCP may better identify patients who would benefit from therapeutic ERCP.

Endoscopic retrograde cholangiopancreatography (ERCP)

ERCP is considered to be the most sensitive and specific test available for the diagnosis of chronic pancreatitis, and this technique has been the gold standard against which all other tests are evaluated. Most studies indicate that the sensitivity and specificity of ERCP range from 70% to 100%.[45–50]

The most commonly used ERCP classification of chronic pancreatitis is the Cambridge classification, which is based on abnormalities seen in the main and side branches of the pancreatic duct. ERCP involves the endoscopic injection of contrast into the pancreatic duct via the papilla of Vater for fluoroscopic imaging. ERCP ductal changes are graded from normal to severe (class IV) (Cambridge classification)[48] (Table 2). However, in current clinical practice, ERCP is rarely performed solely for the diagnosis of CP given invasiveness, high inter-observer and intra-observer variations, and a high risk of complications.

Table 2
Cambridge classification of chronic pancreatitis by endoscopic retrograde pancreatography.

Grade	Main pancreatic duct	Side branches
Normal (grade 0)	Normal	Normal
Equivocal (grade 1)	Normal	< 3 Abnormal
Mild (grade 2)	Normal	> 3 Abnormal
Moderate (grade 3)	Abnormal	> 3 Abnormal
Severe (grade 4)	Abnormal with at least one of the following: Large cavity > 10 mm Duct obstruction Intraductal filling defect Severe dilation or irregularity	> 3 Abnormal

Endoscopic ultrasound (EUS)

Endoscopic ultrasound (EUS) was initially developed for improving the imaging of the pancreas.[51,52] EUS helps to identify features of mild/early disease prior to the development of calcifications, large duct obstruction, and atrophy.

Accuracy of EUS diagnosis in CP relies on quantitative and qualitative parenchymal and ductal criteria.[53] EUS has the ability to detect subtle early changes that may not have been appreciated with other imaging modalities. These include hyperechoic margins of the pancreatic duct, subtle lobularity of the parenchyma, visible side branches with ectasia, and small cystic changes in the parenchyma. There is increasing evidence that these early changes detected by EUS correlate with histology and predict progression to more overt disease.[54–57] There were various scoring systems to diagnose CP which include between 9 and 12 features, and the number of features required to diagnose CP lack standardization.[53] High inter-observer variation of EUS features has been reported in some studies.[58,59]

An international group of experts developed a consensus report entitled "EUS-Rosemont criteria" at the Rosemont Hotel in Chicago, Illinois, in April 2007.[60] The main aim was to design a consensus-based standardized scoring system for CP and to assign weightage to previously described criteria. The individual ductal and parenchymal criteria were classified as major (A or B) or minor criteria of which 8 were identified[60] (Table 3 and Figs. 4–7).

CP diagnosis was classified as consistent, suggestive, or indeterminate[60] (Table 4).

Most centers use at least 5 EUS criteria to diagnose CP.

Table 3
EUS-Rosemont criteria for chronic pancreatitis.

Parenchymal features		
Major A:	**Minor:**	
• Hyperechoic foci with shadowing (B and T)	• Lobularity and no honeycombing (i.e., non-contiguous) • Hyperechoic foci and no shadowing • Cysts • Stranding	
Major B:		
• Lobularity with honeycombing (B and T)		
Ductal features		
Major A:	**Minor:**	
• MPD calculi in H/B/T	• Irregular MPD contour • Dilated side branches • MPD dilation > 3.5 mm in B and > 1.5 mm in T • Hyperechoic duct margin	

MPD—main pancreatic duct; H—head; B—body; T—tail.

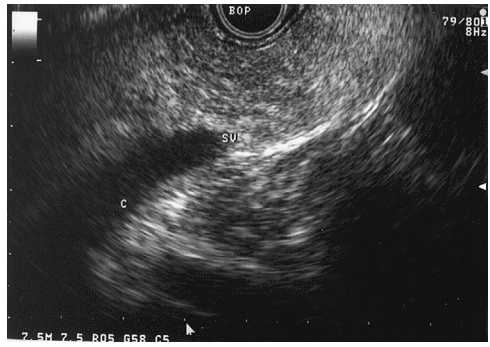

Fig. 4. Normal body of pancreas, finely granular, mixed echogenic parenchyma. SV—splenic vein; c—confluence (salt and pepper pattern). (Adapted with permission from Catalano et al.[60])

Limitations of with the EUS diagnosis of CP

EUS is a highly operator-dependent imaging modality. Postprocedure documentation is often cumbersome and lacks standardization. Inter-observer variation persists, and Stevens et al.[61] noted that using Rosemont classification did not increase the inter-observer agreement when compared with standard scoring. However, a more recent Italian study shown that the Rosemont criteria is accurate, and the overall agreement with standard criteria is fair.[62]

In some cases, EUS being overly sensitive may give false-positive results. In a large study of 2614 patients who underwent EUS for pancreatic disease, Petrone et al. noticed 1 EUS feature of CP in 17% patients. It is unclear if the findings are due to early CP or just age-related changes, or effects of smoking and alcohol.[63] Though EUS is an excellent imaging modality and correlation with acinar and duct-cell function decreases has been demonstrated with very good specificity than with secretin ePFTs, the diagnosis of an early CP may still remain elusive.[64]

Beware of escalating false-positive rate of EUS diagnosis of CP.

EUS elastography

EUS elastography is a recent diagnostic tool, which is a real-time EUS-guided modality that analyzes the tissue stiffness of pancreas quantitatively and may aid in the diagnosis of CP. The principle of EUS elastography is “strain,” i.e., the degree to which physical compression of the tissue causes movement or displacement. Diseased tissue due to fibrosis or malignancy gets harder and is less compliant on physical compression with the transducer.[65] Based on the degree

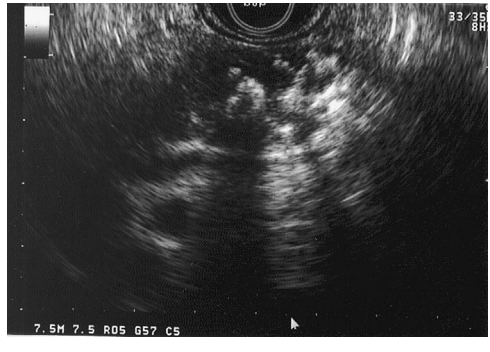

Fig. 5. Hyperechoic foci with shadowing within the parenchyma. (Adapted with permission from Catalano et al.[60])

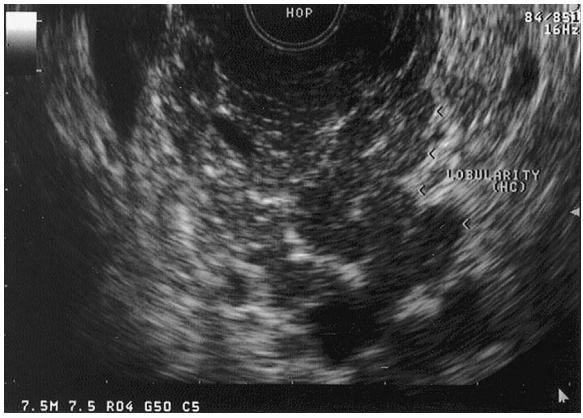

Fig. 6. Pancreatic parenchyma demonstrating honeycombing lobularity. (Adapted with permission from Catalano et al.[60])

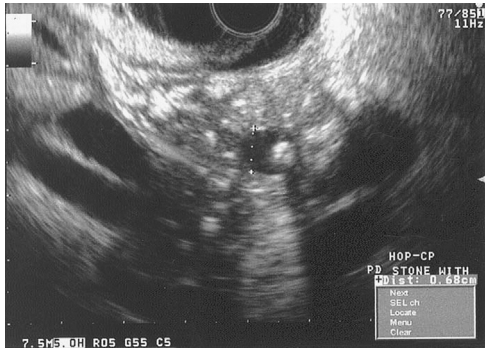

Fig. 7. Dilated pancreatic duct (0.68 cm) with MPD calculi with shadowing. (Adapted with permission from Catalano et al.[60])

Table 4
Rosemont criteria levels of CP assigned.

Consistent with CP	Suggestive of CP	Indeterminate for CP	Normal
1 Major A + ≥3 minor 1 Major A + Major B 2 Major A	1 Major A + <3 minor Major B + ≥3 minor ≥5 Minor	3–4 Minor Major B alone or with <3 minor	3 Or less minor; no major

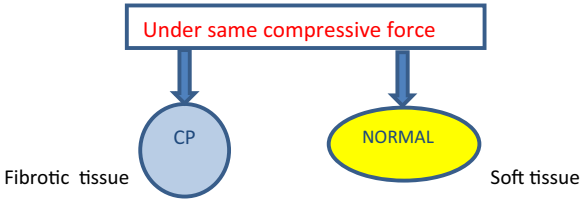

Fig. 8. Principle of EUS elastography.

of displacement, a color pattern is overlaid on the EUS image to create a "color map" corresponding to the stiffness of the tissue[66] (Fig. 8).

Normal pancreas in EUS elastography

Elastographic imaging of the normal pancreas is characterized by a uniform, homogenous green color distribution (representing intermediate stiffness) throughout the organ, and the reproducibility of the signal is relatively good. On qualitative analysis, a healthy pancreas appears to be predominantly green in color with a homogenous (41.7%) or heterogeneous (58.3%) pattern.[67]

EUS elastography in CP

Quantitative elastography shows diagnostic sensitivity and specificity of 91%, and the strain ratio obtained during EUS showed an excellent accuracy for the diagnosis of chronic pancreatitis. EUS elastography also allows quantification of the degree of pancreatic fibrosis and thus evaluation of the severity of the disease. A continuous increase of the strain ratio is seen, as the number of EUS criteria of chronic pancreatitis increases.[68] In a recent study from Spain, it has been shown that the degree of fibrosis as measured by EUS elastography allows quantification of the probability of PEI in patients with CP.[69]

Complications of chronic pancreatitis

Pancreatic pseudocyst

A pseudocyst is a collection of pancreatic fluid, outside the ductal system, that is enclosed by a fibrous tissue membrane. As the fluid cavities are not lined with an epithelium, pseudocysts are not true cysts and are, instead, surrounded by chronic reactive granulation tissue.[70] Traditionally, a pseudocyst is defined at least after 4–6 weeks, when the walls are mature. It is the most common complication of chronic pancreatitis, occurring in up to 25% of cases.[71] Most chronic pseudocysts occur in patients with alcoholic chronic pancreatitis, and they are found more commonly in the body of the pancreas than in the head or tail.[72,73] The therapeutic approach to a pancreatic pseudocyst is dependent upon an accurate diagnosis and a clear understanding of the pathogenesis of the underlying disease. The pathogenesis of initial formation of pseudocysts is still unclear. Possibilities include rupture of the pancreatic duct, necrosis of surrounding parenchyma, leakage of pancreatic fluid into the lesser sac, and local tissue mesothelial reaction.

Pseudocysts develop insidiously in the setting of CP as chronic fluid collections that consist of pancreatic secretions and inflammatory debris. Small pancreatic pseudocysts are usually intrapancreatic and have a thin wall, whereas large pseudocysts are usually in continuity with the pancreas and in due course they may become very large and become remote from the pancreas.

Clinical presentation of pseudocysts

Abdominal pain

Most pseudocysts remain asymptomatic and uncomplicated. Pain is the predominant symptom. Pseudocyst formation should be suspected in a patient with stable chronic pancreatitis who presents with worsening of abdominal pain. The larger the pseudocyst, the more likely it is to cause pain due to compression of adjacent structures.

Gastric dysmotility

Patients may also report early satiety, nausea, and post-prandial vomiting. Deformity of the distal stomach and duodenum may develop due to compression from a pseudocyst or chronic inflammation related to chronic pancreatitis.

Infection of pancreatic pseudocysts

Infection is relatively common, and the origin is presumed to be the migration of enteric organisms from the intestinal tract.[74] The infection could be mild or severe (worsening to sepsis), and drainage is required.[75] Indications for drainage and further management will be discussed in detail below.

Acute gastrointestinal bleeding—Pseudoaneursym

Other complications of pseudocysts include digestion of an adjacent vessel wall that can result in a pseudoaneurysm, which can produce massive gastrointestinal bleeding and bleeding into the pancreatic duct (hemosuccus pancreaticus).[76,77] Pseudoaneurysms may be identified with contrast CT imaging and are seen within the pseudocyst wall in 10% of patients.

Splenic vein thrombosis

Splenic vein thrombosis is a common complication of acute and chronic pancreatitis and may be associated with pancreatic pseudocysts located in the body or tail of the pancreas[78] due to splenic vein compression. Splenic vein thrombosis will result in dilation of the short gastric veins, leading to gastric varices and splenomegaly. Extension of the thrombus into the portal vein is rare, though more commonly seen following necrotizing acute pancreatitis.[79] There is limited evidence to recommend anticoagulation in porto-splenic thrombosis as the course is usually benign.[79] Rarely, splenic artery embolization followed by splenectomy is required to manage GI bleeding from acute isolated gastric varices.[80–82]

Pancreatic ascites and pleural effusion

Pancreatic ascites and pleural effusions can result from disruption of the pancreatic duct, leading to fistula formation to the abdomen or chest, or may be due to rupture of a pseudocyst with tracking of pancreatic fluid into the peritoneal cavity or pleural space. Analysis of fluid obtained at paracentesis or thoracentesis is diagnostic, with a very high amylase concentration, typically >1000 IU/L.[83] Nonoperative methods of management include repeated paracentesis, stenting of the pancreas duct, diuretics, octreotide, or total parentral nutrition.[84] Further management will be discussed in detail below.

Biliary obstruction

Biliary obstruction in CP patients may result from obstruction of the pancreatic–biliary ducts from a pseudocyst located within the head of the pancreas. The most common cause of biliary obstruction is stricture formation in the distal common bile duct due to recurrent inflammation and direct fibrotic reaction secondary to CP. Obstruction of the distal bile duct with resulting jaundice may occur. Drainage of a pseudocyst will often resolve the obstruction of the duct, particularly the bile duct.

CT is the most accurate method of diagnosing pancreatic pseudocysts. Chronic pseudocysts are seen with CT scan as low-attenuation lesions within or adjacent to the pancreas and are commonly round and surrounded by a thick, dense wall. Large pseudocysts may appear in the mediastinum, pelvis, or involve the mesentery. Although pseudocysts are most commonly unilocular, fibrotic strands within the cavity may cause multiple septations. The pseudocyst cavity may also contain debris, blood, or infections that appear as high-attenuation areas within the fluid-filled cavity. Cystic neoplasms of the pancreas may be easily mistaken with CT scanning as pancreatic pseudocysts.[85]

Traditionally, pseudocysts were managed by elective drainage if the pseudocyst was greater than 6 cm after a 6-week observation period.[86] However, with improved understanding of the

natural history of pseudocysts, it is now clear that the vast majority of pseudocysts resolve spontaneously and should not be drained unless there are complications or persistent symptoms.

Management of chronic pancreatitis

Management of chronic pancreatitis is very challenging. As we know the most commonly disabling component of CP is pain, which is often very difficult to treat. Optimal management of PEI and other complications is often challenging.

One of the main reasons for the difficulty in achieving adequate treatment goals in CP is the markedly heterogeneous nature of the disease. One treatment certainly does not suit all patients. The first step in management is to identify the etiology based on TIGAR-O classification and to try to institute a personalized therapy.[87]

Heterogeneity in CP population

1. Etiology: alcohol vs non-alcohol
2. Obstruction vs no obstruction
3. Dilated main pancreatic duct vs minimal change CP
4. Active inflammation vs quiescent inflammation

Management of pain

Abdominal pain is the most common feature of CP. Pain in CP is detrimental to quality of life and may cause both physical and emotional disability.[88] CP-related pain is typically chronic and continuous.[89] Recent studies focused on understanding and treating neuropathic pain, which is described in part-I of this review.[90]

Therapeutic approaches to pain: General measures

Abstinence from alcohol and smoking

The important goal of therapy in CP is to slow the natural progression of the disease. This involves directed efforts to achieve abstinence from alcohol and smoking.[91] It has been shown that abstinence not only slows the progression of the disease but also prevents the emergence of complications such as cancer.[92]

Analgesics

The main stay of treatment of pain is medical therapy with analgesics. Most patients with pain will require analgesics. Several epidemiological studies estimate that approximately half of all patients with chronic pancreatitis will be treated with opioids. Most studies show that addiction risk is approximately 20% in any chronic pain syndromes. In patients with significant prior alcohol or smoking use, the drug dependency and abuse potential are increased.[93]

It is prudent to start with less potent opioids. Tramadol is commonly used in dosages of 200–400 mg daily, although most patients ultimately require more potent narcotics.[94–96] Along with narcotics, a number of other agents have been used to treat CP pain, such as tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and gabapentinoids with limited success.

Among these drugs, only pregabalin has been studied in a randomized controlled trial in patients with chronic pancreatitis.[97] A study of 64 patients with CP showed that quantitative sensory testing predicts the analgesic effect of pregabalin in patients with painful chronic pancreatitis.[98] In a placebo controlled trial, patients treated with pregabalin (up to 300 mg twice daily) had reduced pain and were able to reduce opioid use,[97] highlighting the central nature of CP pain.

Pancreatic enzyme therapy for pain—PERT decreases CCK-mediated stimulation

PERT has been widely utilized in treating pain in CP patients. The pathophysiologic rationale behind the use of PERT in pain relief is their ability to degrade CCK-releasing factor in the duodenum and by doing so, lowering CCK levels, and through this mechanism, reducing pain.

PERT → inhibit duodenal CCK release → ↓ pancreatic secretion → ↓ ductal pressure

Only non-enteric coated (i.e., tablet) formulations have this activity, and studies using this type of enzymes have demonstrated improvement in pain.[95,99,100] Interestingly, studies using enteric coated preparations (which are not active in the duodenum and hence cannot degrade CCK-releasing factor) have not shown similar results.[101–103] From the NAPS2 study, among 516 well-phenotyped CP patients with pain, PERT was useful for pain relief in only a very small subset of CP patients.[104] A meta-analysis using both types of enzyme formulation noted no effect of enzymes.[105] In several well-conducted randomized trials with crossover designs, the results were mixed. These studies had significant heterogeneity in patient selection, enzyme dosage and formulation, and outcome measures.[106] In general, enzyme therapy is most likely to be effective in those with "small duct" or "minimal change" CP. If PERT is used for achieving pain relief, we would recommend using non-enteric coated enzymes along with a proton pump inhibitor to reduce acid degradation and reach the duodenum. The dose is the equivalent of 16,000 USP lipase, 60,000 protease, and 60,000 amylase (4 tablets a day) with meals and snacks, and the therapeutic trial should last at least 6 weeks.

Use non-enteric coated pancreatic enzymes along with PPIs, if PERT is administered for pain relief.

Antioxidant therapy for pain relief

Several antioxidants such as selenium, vitamin C, β-carotene, vitamin E, and methionine are being used in pain management in CP patients without clear evidence. It is believed that the free radicals causing oxidative stress may play a role in pancreatic injury, and antioxidants would defend against them. Two well-conducted large randomized trials showed different results. The trial that demonstrated beneficial response included much younger patients mainly with idiopathic CP, in contrast to the trial with negative results, which included older patients with alcohol and smoking as primary etiologies.[107,108] Though there are several studies that were inconclusive, recent meta-analyses show some marginal benefit.[109] A meta-analysis of 9 RCTs looked at combined antioxidant therapy and found that to be safe and a more effective therapy for CP pain relief than using a single antioxidant agent.[110] Antioxidants appear to be risk-free, and a trial of these may not be unreasonable, though further studies are needed to define the patient population most likely to respond.[94]

- Evidence for the use of antioxidants for pain relief is inconclusive.
- Trial of combined antioxidants in younger idiopathic CP patients is reasonable.

Octreotide therapy

Octreotide, a synthetic somatostatin analog, has been tried in the management of CP pain with insufficient supporting data. It is thought to suppress CCK and secretin and thereby suppress pancreatic secretion. While pilot studies and animal models showed effectiveness, other studies did not.[111] With chronic pancreatitis patients at risk for developing type 3c diabetes mellitus, we would not recommend using octreotide with such insufficient evidence.

Octreotide is not useful in pain management in CP patients.

Newer areas of research

Chronic pancreatitis pain syndromes are difficult to manage, and research on additional pain reduction therapies is needed. A recent trial studied the use of a defective Herpes (HSV-1, DPE) viral vector construct encoding the human pre-proenkephalin gene (HSV-Enk) as a molecular therapy for alleviating pancreatitis pain.[112,113]

Newer areas of research in chronic pancreatitis pain management
1. Gene therapy
2. Synthetic pancreatic enzymes
3. Anti-nocciceptive therapy
4. Mast cell-directed therapy
5. Nerve growth factors
6. Anti-fibrogenesis therapy
7. Treatment with central and peripheral pain sensitization
8. Secretin stimulation "wash-out"
9. Radio-frequency ablation and spinal stimulation

The placebo response rates in CP pain management trials may be up to 20%.[114]

Management of PEI and malabsorption

Pancreatic enzyme replacement therapy (PERT) is the cornerstone in the treatment of PEI and malabsorption in CP. Any CP patient who experiences weight loss and those with relevant PEI symptoms such as steatorrhea are candidates for PERT.

Exogenous pancreatic enzymes are safe and well tolerated. The enzyme preparations are composed of porcine lipase (Lipase U/mg is the main constituent), amylase, and protease. Pancreatic enzyme preparations (PEP) differ based on dosage in enzyme content, the use of microspheres vs micro-tablets, and the presence of an enteric coating for delayed release. A minimum of 20,000 U lipase per meal is the dose to be started initially. This dose allows adequate intraluminal digestion of fat and protein in most patients.

There are 6 PEPs approved by FDA, namely Creon, Zenpep, Pancreaze, Ultresa, Viokace, and Pertzye. All these products are enteric coated except Viokace®, which is non-enteric coated and mainly used when treating pain in CP patients.[115] Lipase is sensitive to degradation by acid, so the non-enteric coated product Viokace requires co-treatment with an agent to suppress gastric acid, such as an H2-blocker or proton pump inhibitor.

Only non-enteric coated formulation of PEP (with PPI) is preferred when treating pain in CP.

Creon, Zenpep, and Pancreaze are the 3 delayed-release products that have demonstrated efficacy and safety in EPI.[116] Creon has also demonstrated safety and efficacy in EPI secondary to chronic pancreatitis and pancreatectomy. There is not much cost difference between the 3 products. Currently, the FDA-approved Pertzye® is the only bicarbonate-buffered pancreatic enzyme available. Adverse events for all PEPs were less than or similar to those with placebo in all the clinical studies, and these agents are very well tolerated. The main problem during therapy is patient compliance.

Appropriate dose is the key in management of PEI. The healthy human pancreas produces approximately 900,000 USP units of lipase with each meal and that approximately 10% of this amount is necessary to achieve relatively normal absorption of fat and fat-soluble vitamins. Therefore, about 90,000 USP units of lipase per meal are needed for adequate fat absorption. However, in most patients, the pancreas still has some residual capacity to produce some lipase, and therefore a full 90,000 USP units per meal is not always required.

Although the enzyme dose should be individualized for each patient, most patients require a minimum dose of 40,000–50,000 USP units of lipase per meal and half amount, i.e., 20,000–25,000 USP units, per snack. The dose is titrated based on clinical response (decrease in diarrhea, increase in body weight, and serum levels of fat-soluble vitamins), and dose can be increased to as much as 90,000 U lipase per meal.

Regarding timing of therapy, studies have demonstrated that the efficacy of the enzyme substitution therapy is higher when enzymes are administered during meals rather than just before meals.[117]

A diet containing less than 50–75 g of fat daily was generally recommended. However, restriction of fat intake is linked to insufficient intake of fat-soluble vitamins (which are already malabsorbed in patients with pancreatic exocrine insufficiency) and malnutrition. As a consequence, fat restriction is no longer considered necessary in the management of patients with pancreatic exocrine insufficiency.

Macronutrient replacement

Although pancreatic exocrine insufficiency can interfere with digestion of fats, proteins, and carbohydrates, the effect is most pronounced on fat and fat-soluble vitamin absorption. Even in sub-clinical stage, CP patients have significant osteoporosis, and there is high prevalence of low-trauma fractures in CP.[118] While fat-soluble vitamins such as A, E, and K are sufficient, vitamin D along with calcium should be supplemented routinely (calcium 1200 mg and vitamin D 800 IU daily). Zinc, magnesium, and folate deficiencies are also seen in CP patients and are commonly overlooked.

- A minimum dose of 40,000–50,000 USP units of lipase per meal and half the amount, i.e., 20,000–25,000 USP units, per snack are required in treating PEI.
- Addition of PPI increases the efficacy in all PEPs and is mandatory with uncoated enzymes.
- A very low-fat diet is not recommended.

Chronic pancreatitis—When to scope?

Endoscopic intervention in CP

Indications for endoscopic intervention are diagnostic and therapeutic. Diagnostic considerations of endoscopy using EUS, ERCP, and ePFT have been discussed above. Although the Cambridge classification is a well-established ERCP criteria, ERCP has a limited diagnostic role in modern practice.

EUS interventions

EUS-guided celiac plexus block

Endoscopic ultrasound (EUS)-guided celiac plexus block (CPB) and celiac plexus neurolysis (CPN) have a well-established role in the control of pain due to pancreas malignancy; however, their role in the management of pain due to chronic pancreatitis remains debatable.

Although celiac plexus block can be performed percutaneously with CT guidance, EUS-guided CPB may last somewhat longer.[119] Based on a small uncontrolled study, only half the patients who undergo CPB for CP get pain relief and that too is often transient, on average 2–4 months.[120] Given the limited data, use of EUS-CPB for CP is controversial.

Trans-gastric EUS well visualizes the region of the celiac plexus, and EUS-guided CPN can be easily and safely performed with lower complications vs a posterior approach (Fig. 9). Celiac plexus blockade (CPB) typically involves the injection of bupivacaine and a steroid, while CPN utilizes bupivacaine and alcohol injection. Technical variations include injection at a central single site, bilateral injections lateral to the celiac ganglia, injection over the SMA,[121] and/or injection directly into celiac ganglia. Sahai et al.[122] compared unilateral with bilateral injection in a mixed population of patients with pancreatic cancer or chronic pancreatitis and found bilateral injection to be more effective.

In a pooled analysis of data from 8 studies, EUS-CPN provided pain relief of 80% and 59% in pancreas cancer and chronic pancreatitis, respectively.[123] A meta-analysis with 221 patients found that EUS-guided CPB was 51.5% effective in managing chronic abdominal pain in patients with chronic pancreatitis, but warrants improvement in patient selection and refinement of

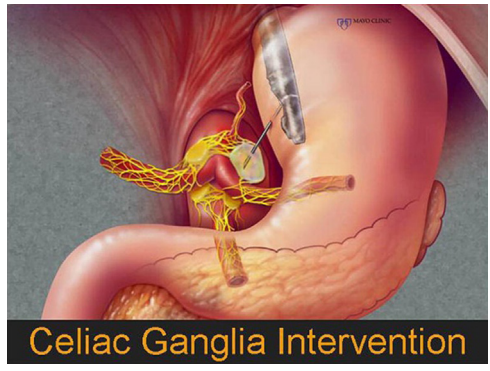

Fig. 9. EUS-guided celiac ganglia plexus block.

technique, whereas EUS-guided CPN was 72.5% effective in managing pain due to pancreatic cancer and is a reasonable option for patients with tolerance to narcotic analgesics.[124]

- Controversies in EUS-CPN—1 sided vs 2 sided, Ganglia injection or not, inject between SMA/celiac
- Pain relief from CPN/CPB is temporary
- EUS-CPB/CPN is currently not recommended as routine endoscopic therapy for pain control in CP

EUS drainage of pancreatic pseudocyst

Endoscopic drainage of pancreatic fluid collections has become an established alternative to surgical treatment. Endoscopic drainage has a potential risk of hemorrhage of approximately 6%, and this risk further increase when there is no visible bulge seen intraluminally.[125,126] EUS has an important role in the drainage of pancreatic pseudocysts safely due to the identification of interposed vessels and unappreciated debris within the collection.[127–129] A meta-analysis by Panamonta et al. including 229 patients found EUS-guided drainage to be similar to a conventional endoscopic approach in terms of short-term success and complication rates for bulging pseudocysts.

EUS-guided drainage, however, was noted to be the treatment of choice for non-bulging pseudocysts, and in the setting of portal hypertension, or coagulopathy.[130] EUS allows accurate measurement of the distance between the gut lumen and the cyst cavity; a distance of more than 1 cm is considered a contraindication to drainage.[131] Transmural EUS-GD may be safely performed even in the absence of a visible intraluminal bulge, if the cyst is adherent to the intestinal wall.[132,133] Potential complications of pancreatic fluid collection drainage include hemorrhage, perforation, infection, stent migration, and incomplete drainage.[134]

ERCP intervention—Pancreatic endotherapy

ERCP may be useful in relieving pain in CP patients by a variety of mechanisms. The goal of ERCP-based endotherapy is to achieve complete duct clearance by alleviating outflow obstruction of the main pancreatic duct (from stones or strictures), evacuate focal fluid collections, and divert the flow from a fistula or a pancreatic duct leak.[135–138]

Endoscopic ductal decompression therapy has become an established method of treating patients with painful obstructive chronic pancreatitis. However, even if duct clearance is achieved, the clinical response is variable.[138] In a large study of >1000 patients who had been selected for endoscopic treatment of painful CP, main pancreatic duct (MPD) obstruction is caused by pancreatic stones alone, ductal strictures alone, and a combination of stones and strictures in 18%, 47% and 32% of cases, respectively. Endoscopic MPD drainage yielded similar results in these different categories of patients, with 51.4% of patients having no pain at all at a mean follow-up of 4.9 years.[139]

Endoscopic pancreatic sphincterotomy (EPS)

EPS is a well-known mode of therapy and could offer symptomatic relief in a variety of pancreatic disorders including, chronic pancreatitis, and pancreas divisum. Some of the patients with mild CP as defined by Cambridge classification may present with persistent pain. In a small retrospective study of 11 early-onset CP patients, more than two-thirds of patients had good pain relief following EPS.[140] In patients with chronic pancreatitis, EPS with a standard sphincterotome or with a needle-knife offers an effective and reliable approach to the pancreatic duct system, and complication rate of EPS in CP patients appears to be lower than the complication rate of biliary sphincterotomy for other indications.[141] When compared to EPS with a pull sphincterotome (followed by pancreatic stenting) or a needle-knife over a pancreatic stent, EPS is safer when performed with a needle-knife over a pancreatic stent.[142] The common expected complications of EPS are post-ERCP pancreatitis, bleeding, perforation, and restenosis. In a large study of 398 patients who underwent EPS, post-ERCP pancreatitis was minimized with either pancreatic duct stent placement or nasopancreatic drainage.[143] EPS in CP patients has shown to have 14% restenosis during a 4-year follow-up.[144] When performing EPS for pain relief in CP, routine biliary sphincterotomy is not indicated unless the common bile duct is dilated or there is an elevation of alkaline phosphatase.[145]

Minor papilla sphincterotomy in CP patients

The benefit of minor papilla sphincterotomy is dependent upon the clinical setting. Lehman et al.[146] reported that minor papilla sphincterotomy helps acute recurrent pancreatitis more frequently than those with chronic pancreatitis (76.5% vs 27.3%, $p = 0.01$). Vitale et al.[147] followed 24 CP patients with pancreas divisum and reported significant pain relief on 2-year follow-up following minor papilla sphincterotomy and stenting. A recent Japanese study showed that endoscopic balloon dilation (EBD) of the minor papilla is feasible and effective for management of symptomatic pancreas divisum in CP patients.[148]

Management of pancreatic duct strictures in CP

Management of strictures secondary to CP is often challenging. Along with pancreatic duct strictures, patients often present with distal biliary strictures resulting from ongoing inflammation and fibrotic reaction. The most important initial aim is to rule out malignancy. As CP is associated with an increased risk of pancreas cancer, one should always reasonably exclude pancreatic cancer if a MPD stricture is detected, particularly in the absence of pancreatic calcifications and in the presence of exocrine insufficiency or new late-onset diabetes, without smoking or alcohol history.[149,150] It has been shown that approximately 5% of patients with pancreatic cancer are initially misdiagnosed as CP.[151]

Traditionally, plastic stents made of Teflon, polyethylene, or polyurethane are used, and these stents are easily exchanged. If MPD obstruction is caused by stricture(s), insertion of single plastic stent is effective but requires multiple ERCPs for stent exchanges and dilation of the stricture.

Stricture dilation and a single plastic stent

ERCP intervention (endotherapy) is ideal for single strictures in the head, while isolated strictures in the tail or multiple strictures in the body with a chain of lake appearance are not usually amenable to endotherapy.[152]

In the past, dilation alone was used to treat single strictures, but in current practice, dilation alone has rarely been an adequate treatment. Dilation is routinely followed by placement of plastic pancreatic stents. On relieving MPD stricture obstruction, pain relief was reported at short- and long-term follow-up in 70–94% and 52–82% of patients, respectively.[152,153] Leaving

the PD stent for short terms (6 months) alone frequently does not yield an adequate clinical response, and stents are often needed for a longer duration.[154] Prior to stent placement, tight strictures sometimes need to be dilated with Teflon bougies, a Soehendra stent retriever, or a balloon dilator.[155] Plastic stents are placed across the stricture and typically exchanged every 3 months. Large-bore stents of size 7–10 Fr are progressively used while treating MPD strictures. The stent size is usually limited by the unaffected downstream duct (close to the pancreas head). Commonly, stent exchanges are performed for about 24 months.

Criteria used for "definitively" removing a stent (with no intent to replace the stent again) usually consist of (1) adequate outflow of contrast medium into the duodenum within 1–2 min after ductal filling upstream from the dilated stricture, immediately after stent removal plus extraction of ductal debris, and (2) easy passage of a 6-Fr catheter through the dilated stricture.[136]

The mean delay of recurrence of pain after definitive removal is around 2.1 years. After definitive stent removal, recurrence of symptoms and strictures was reported in 27–38% of patients after 2 years of follow-up.[156] The most important factor associated with higher restenosis rates in CP patients is the presence of pancreas divisum.[156]

Multiple plastic stenting

Costamagna et al.[157] proposed using multiple plastic stenting for MPD strictures not responding to a single stent placement. In their study of 19 patients who had a MPD stricture that persisted immediately after removal of a single pancreatic stent, multiple plastic stents (8.5–11.5-Fr diameter) were placed. On an average, 3 stents were used, and the stents were removed after a mean of 7 months. Stricture resolution was seen in 95% and pain relief in 84% on a 38-month follow-up.[157] The main advantages of this technique include a low number of ERCP sessions (2) and a large dilation diameter that might account for the absence of pain relapse during a relatively long follow-up. However, further prospective controlled studies are needed to confirm these promising results.

Self-expandable metal stents

When compared with plastic stents, self-expandable metal stents (SEMS) present 2 main advantages: a relatively easy insertion as they have small-diameter delivery systems and a large luminal diameter. SEMS are not approved by the FDA for use in benign strictures due to CP but are occasionally used off-label for this indication. Due to tissue in-growth, only fully covered SEMS (FCSEMS) are used in PD strictures. Poley et al.,[158] in a study of 13 CP patients, demonstrated better results using FCSEMS when compared with progressive plastic stenting protocols. A major limitation of FCSEMS is frequent stent migration (5–33%). In order to reduce the risk of migration, anti-migration features such as anchoring flaps and flared ends were introduced, and these modified stents have been studied in MPD strictures in CP patients by Moon et al.[159]

In a recent prospective study of 17 patients with FCSEMS (Niti-S; Taewoong Medical) for biliary strictures caused secondary to chronic pancreatitis, the initial patients had stents with unflared ends and had migrations rates of 100%. The remainder of the patients received stents with flared ends resulting in decreased distal migration rates of 40%. The stricture resolution rate for patients using flared ends (10 patients) at the time of stent removal was 90% and 80% after 12 months of follow-up.[160]

With a paucity of controlled data, further trials are needed to assess the long-term safety and efficacy of using FCSEMS in intrapancreatic biliary strictures and PD strictures in the setting of CP.

- Malignancy should be ruled out in duct strictures, especially the absence of pancreatic calcifications, smoking or alcohol history, and presence of new late-onset diabetes.
- Single plastic stenting with multiple exchanges over 2 years is effective.
- Multiple plastic stent insertion and FCSEMS look promising, and further larger studies are required.
- The success of PD stenting can be measured as pain relief >2 years after "definitively" removing the stent.

Pancreatic duct stone management

Pancreatic ductal calculi are often seen in CP and cause pain by obstructing pancreatic ducts and producing upstream ductal hypertension. Stones seen in tropical pancreatitis and hereditary pancreatitis are somewhat larger than that seen in alcoholic CP. Larger size makes endotherapy difficult, whereas stones < 5 mm are more amenable to endoscopic extraction after pancreatic sphincterotomy. However, in 70–90% of cases, pancreatic stones cannot be extracted without pre-ERCP fragmentation (by mechanical and/or extracorporeal shock wave lithotripsy [ESWL]).[135,161]

Extracorporeal shock wave lithotripsy

ESWL is now accepted as the standard of care in the management of large PD calculi not amenable to routine endotherapy.[162,163] ESWL is very effective in fragmenting both radio-opaque and radio-lucent calculi in the MPD. A meta-analysis of 17 studies with a total of 588 patients looked at pain relief and duct clearance as the primary end point. They noted a duct clearance rate between 37% and 100% and good pain relief, and a mean effect size (weighted correlation coefficient) for pain was 0.6215 and for duct clearance was 0.7432 (indicates moderate to high practical significance).[164]

ESWL is routinely used in urology for clearance of nephrolithiasis. In many US centers, urologists perform ESWL for PD stones. Components of ESWL machines include (1) a shock wave generator, (2) a focusing system, (3) a coupling mechanism, and (4) a localization unit.[153] Shock waves are generated via piezoelectric technology, and the focusing system concentrates shock waves into a precise target volume that is similar to a cigar, where fragmentation of hard structures will take place. The coupling mechanism between the shock wave generator and the patient's body currently consists of a cushion surrounding the shock wave generator, which is closely applied onto the patient's skin (with a special gel similar to that used in ultrasonography). The localization unit allows maintaining the target stone inside the target volume, using fluoroscopy. The patient is positioned prone or supine with slight tilt to prevent the spine from being located in the target volume.

If there are several stones present, the one located inside the MPD closest to the papilla is targeted first, and then gradually moved to more proximal MPD stones, once distal ones have been fragmented. Usually the stones in tail and the side branches are not targeted as they do not significantly impede the outflow of pancreatic fluid and, if targeted, resulting stone fragments might migrate into the MPD and cause worsening obstruction.[153]

High-energy shock waves are delivered until the stone is fragmented (seen via fluoroscopy), and though there is limited evidence on the maximum number of shock waves that may be administered per session, 5000–6000 are typically performed, and patients are scheduled for further supplementary sessions as needed. In most centers, ESWL is done as an ambulatory procedure under GA, and an abdominal radiograph is obtained 1–2 weeks later to assess the need for further ESWL.

Combining ERCP with ESWL

In many centers, endotherapy is used in combination with ESWL. In a study of 55 patients randomized to ESWL alone or ESWL combined with endoscopy, both groups had similar pain relief (62% vs 55%), and the authors concluded that combining systematic endoscopy with ESWL adds to the cost of patient care, without improving the outcome of pancreatic pain.[162] In another recent study by Cotton et al., combined use of ESWL with endotherapy was shown to prevent pancreatic surgery in the majority of patients.[165] In most studies using ESWL (alone or combined with endoscopic drainage), more than 70–80% of patients had short-term pain relief and about 60% had long-term pain relief (2–5 years).[166–168] ESWL is a relatively safe and well-tolerated

procedure.[169] We recommend using endotherapy to supplement ESWL as required with a focus on appropriate patient selection.

Secretin ESWL

Human secretin injection increases bicarbonate-rich pancreatic fluid secretion. To see if this could facilitate excretion of pulverized pancreatic stones during ESWL, Choi et al.[170] studied 233 consecutive cases and observed that secretin use resulted in significantly higher rate of complete MPDS clearance (63% vs 46%, $p = 0.021$).

- ESWL is the first-line therapy for large MPD stone Head >> Body, and combination with endotherapy is beneficial
- Radio-opaque stone → ESWL fragmentation < 3 mm → ERCP-EPS + PD clearance ± stent
- Radio-lucent stone → ERCP-EPS → ESWL fragmentation < 3 mm → ERCP-EPS + PD clearance ± stent
- EHL is feasible but not an initial line of therapy in PD stones

Intraductal lithotripsy

Lithotripsy is commonly used for biliary stones, but occasionally mechanical lithotripsy is also used in treating pancreatic calcifications (prior to sending for ESWL), because intact pancreatic stones are difficult to seize with a Dormia basket.[161] Electrohydraulic lithotripsy (EHL) within the pancreatic duct using a 10-Fr pancreatoscope has been tried as an adjunctive endoscopic option for treatment of patients with symptomatic pancreatic duct stones.[171]

Chemical dissolution of PD stone

As early as 1979, Sarles et al.[172] described the chemical dissolution of pancreatic stones using citrate. An anti-epileptic drug, trimethadione, has been shown to be efficacious in PD stone dissolution.[173] Noda et al.[174] reported that pancreatic calcifications decreased in size or number (or even disappeared) in 21 (70%) of 30 patients treated with oral intake of trimethadione at a dose of 0.9–1.5 g daily without any serious side effects except mild photophobia.

CP—When to operate?

Surgery plays an important but not an early role in CP management. The indications for surgery are disabling pain, obstructive features, presence of a mass, risk of malignancy, and other local complications such as pseudoaneurysm or erosion of the large vessels, large pancreatic pseudocysts, and internal pancreatic fistula. However, the most common indication for surgery is refractory pain.

The optimal surgical procedure should manage the pain, preserve a maximum of endocrine and exocrine function still present, and restore quality of life. Several surgical options exist for select patients with visceral pain resulting from CP. Three main types of surgical interventions practiced in CP are drainage procedures (decompression), combined drainage and resection, and resection. One of the main determinants of selection of one of these strategies is the size of the pancreatic duct.

Drainage procedures

In patients with a dilated main pancreatic duct, a side-to-side pancreaticojejunostomy (Puestow procedure) may be performed. In 1958, Puestow and Gillesby[175] described distal pancreatectomy with retrograde drainage of pancreas, which was later modified to the current *lateral* pancreaticojejunostomy.[176] The main PD should be > 6–7 mm (at least > 5 mm) to perform this procedure.[177] It is a relatively simple, safe, and effective surgical treatment option

in patients with dilated main PD including the advantage of no resection of pancreatic parenchyma. Some studies have shown a delay in the deterioration of pancreatic function in patients who were treated by pancreaticojejunostomy compared to patients who were treated conservatively.[178]

Combined drainage and resection

Presence of an inflammatory mass in the pancreatic head along with dilation of the main PD would require combined drainage and resection, such as a Frey or a Beger procedure if surgery is attempted. Frey's procedure consists of a pancreaticojejunostomy with coring out the pancreatic head, leaving a narrow rim of pancreatic capsule on the duodenum and the posterior part of the head and adjacent to the portal and mesenteric veins. The combined procedures are aimed at drainage of the PD, and they also have the advantage of resolution of the biliary tract obstruction (by resection of an inflammatory mass in head) in a single operation.[179] The Beger procedure is almost similar to the Frey, but with more invasive subtotal resection of the pancreas head, followed by the drainage procedure.

Resection-only procedures

Resection-alone procedures for the treatment of CP consists of (pylorus-preserving) pancreaticoduodenectomy, distal pancreatectomy, and total pancreatectomy. Resection is considered when there is no possibility for drainage, and the patient is very symptomatic after all other therapies failed.

Diffuse parenchymal disease may be an indication to consider resection.

Whipple's procedure and distal pancreatectomy

While Whipple's pancreaticoduodenectomy for CP includes the major disadvantage of removal of the surrounding non-diseased organs and major surgical morbidity, distal pancreatectomy is relatively safer.

Most studies of surgical and endoscopic decompressive therapy in CP have revealed good short-term (80%) but poor long-term pain control (40% relapse in 2 years). In patients with large dilated duct obstructive disease, surgery seems to be superior to endoscopic therapy.

Cahen et al.[180] in his randomized control trial showed that surgery relieved pain in a significantly greater proportion of patients than endoscopic treatment. In this study, the endoscopic therapy was more complex and included ESWL if needed and the use of larger caliber pancreatic duct stents. The surgical therapy was a lateral pancreaticojejunostomy (modified Puestow operation). Cahen et al.[181] in their subsequent study also showed that benefit from surgery was durable at 5 years, and patients assigned to surgery required less number of procedures. These results endorsed the early reports of durability of surgical intervention when compared to endotherapy.[182] NAPS investigators studied 515 CP patients and noted that surgical therapies were performed less frequently than endoscopic therapies but were more often reported to be effective (Fig. 10).

The AGA technical review has stated that surgical procedures are best performed based on "need for long-term narcotic therapy, marked diminution of the quality of life because of intractable pain, or major nutritional consequences of pain." Though long-term benefits have been shown with surgery, there remains a role for trying endoscopic therapy initially.[138]

Endoscopic therapy	Surgical therapy
• Short-term relief is better • Urgent indications • Non-surgical candidates	• Long-term relief is better • Elective indication

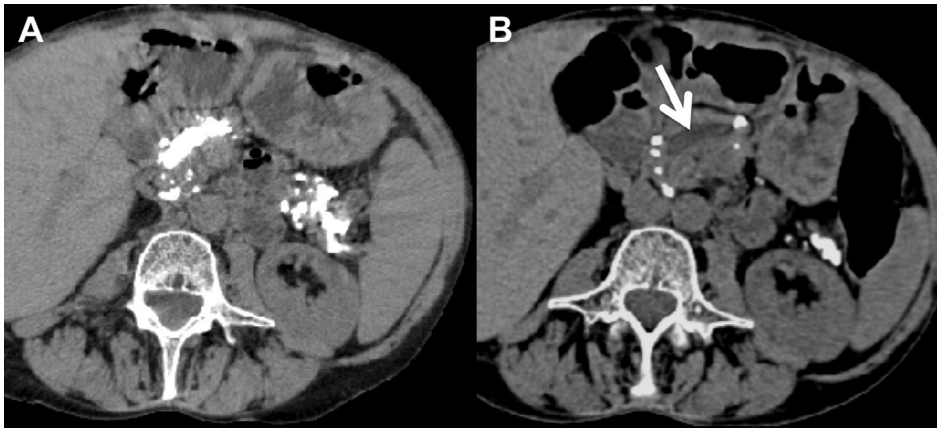

Fig. 10. CT scan of patient with calcific pancreatitis, before and after ESWL. (Adapted with permission from Nguyen-Tang and Dumonceau.[153])

Total pancreatectomy with islet cell auto-transplantation

Total pancreatectomy with islet autotransplantation (TPIAT) is a radical surgical procedure used to treat severe complications of chronic pancreatitis, especially patients with disabling abdominal pain (Fig. 11). The primary indication for TPIAT is to treat intractable pain in patients with impaired quality of life due to chronic pancreatitis in whom medical, endoscopic, or prior surgical therapy has failed.

Currently, TPIAT is available at only a few highly specialized pancreatic centers in the US. Pain relief is not universal with these procedures, and up to 50% may still require narcotics at 1 year.[183] However, a very recent study of 166 patients who underwent TPIAT reported narcotic independence rate at 1 year as 55% and continued to improve to 73% at 5-year follow-up ($p < 0.05$).[184]

TPIAT is not done in patients with active alcoholism, active illicit substance use, or untreated/uncontrolled psychiatric illness that could be expected to impair the patient's ability to adhere to complicated medical management. Also, patients with poor support networks have a relative contraindication due to the cost and complexity of managing diabetes and pancreatic enzyme replacement therapies. After confirming that the pain is from CP, monitoring for the presence of diabetes,[185] assessing β-cell mass,[185] assessing the patency of the portal venous system, and evaluating for liver disease, TPIAT is considered. Lifelong monitoring for diabetes mellitus is needed,

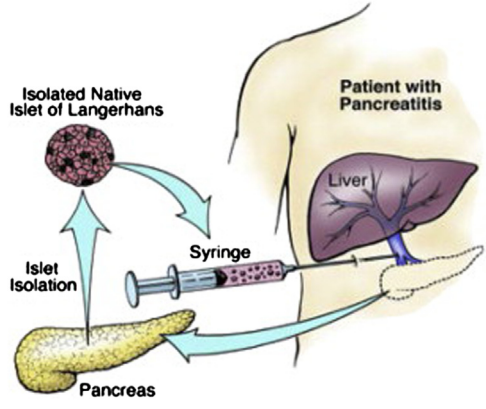

Fig. 11. Total pancreatectomy with islet cell auto-transplantation. (Adapted with permission from Witkowski et al.[187])

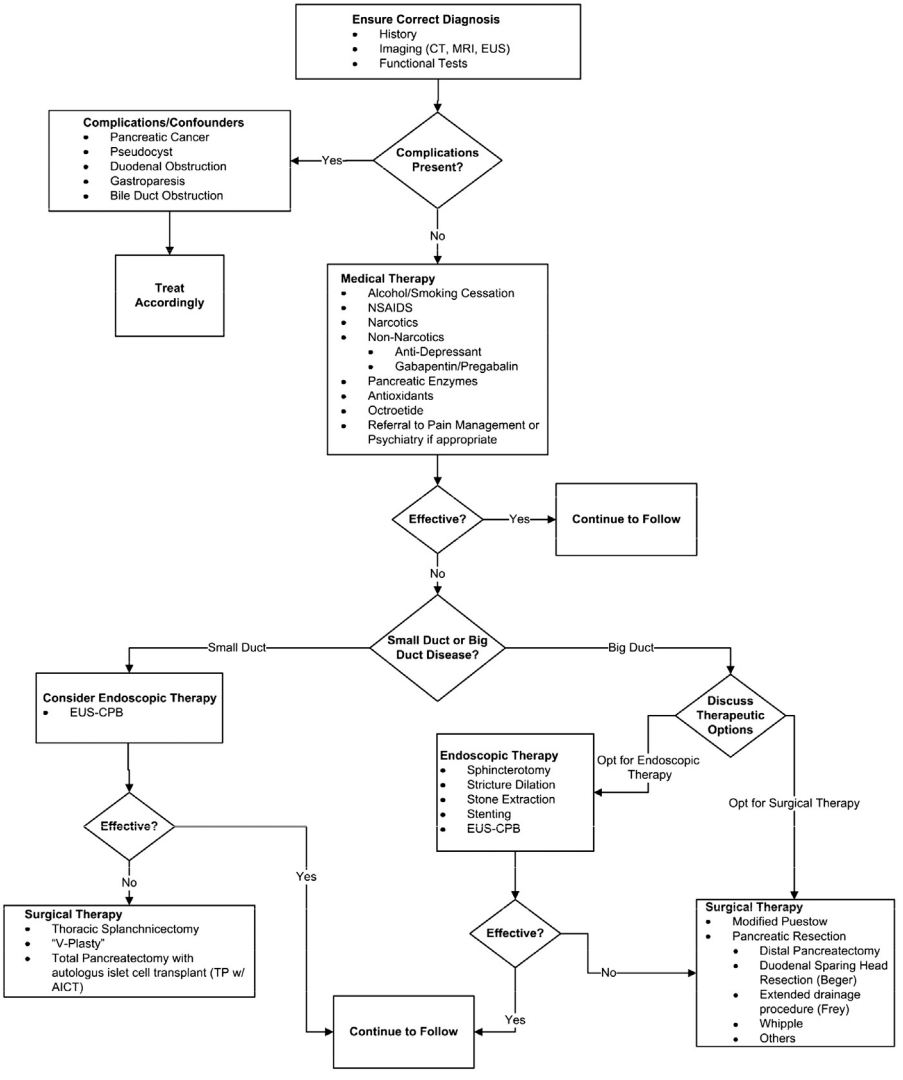

Fig. 12. Algorithm summarizing management of pain in CP. (Adapted with permission Chauhan and Forsmark.[194])

and this includes self-monitored blood glucose, hemoglobin A1c, and also β-cell mass (C-peptide) assessment. Post TPIAT, patients are in lifelong PERT and continue nutrition monitoring.[186]

Because many centers lack access to an islet-isolating facility, there is recent proposal of using a remote regional center collaboration to remotely isolate cells, and perform TPIAT in their own centers.[188] Also, TPIAT is now increasingly performed for minimal change CP (MCCP) and shown as cost-effective as well.[189,190] While this is an interesting and good option for MCCP patients who were poorly managed, we should remember the risk of over-diagnosing non-CP abdominal pain patients as MCCP with modern high-definition EUS probes. TPIAT in such scenarios would cause extreme unwanted morbidity to patient.

- Beware of false-positive MCCP while referring patients for TPIAT.
- Overall, 75% patient with islet autotransplantation might still need insulin, but "brittle diabetes" is avoided.

Management of endocrine insufficiency—Type 3c pancreatogenic diabetes mellitus

Chronic pancreatitis is a syndrome of pancreatic inflammation with irreversible parenchymal damage, which leads to failure to digest nutrients in the proximal gut, may result in impaired incretin secretion and thereby diminished insulin release; loss of islet cell mass further contributes to pancreatic endocrine insufficiency. This destruction of islet cells in CP differs from that in type 1 diabetes by the loss not only of insulin from islet beta cells but also of glucagon and pancreatic polypeptide from islet alpha and PP cells, rendering the disease as "brittle" diabetes. This type of diabetes is unique and different from type 2 diabetes and classified as type 3c pancreatogenic diabetes.[191–193] While any patient with chronic pancreatitis with long duration of disease should be monitored for development of diabetes, those with prior partial pancreatectomy, and early onset of calcific disease may be at higher risk. Most often the patients developing such type 3c diabetes mellitus are likely to have coexisting pancreatic exocrine insufficiency.[193] It is still unclear, if the patient has such brittle diabetes and planned for TPIAT, whether the insulin or C-peptide response to glucose-potentiated arginine testing is predictive of islet yield.[193]

Summary

Management of chronic pancreatitis is challenging and requires a personalized approach (Fig. 12). Early diagnosis of CP plays a significant role in the natural history of the disease. Appropriate usage of diagnostic tools such as EUS and implementing an individualized therapeutic plan may help achieve a better quality of life for CP patients.

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