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Chronic Pancreatitis

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Introduction

Chronic pancreatitis is a chronic inflammatory disorder of the pancreas that ultimately results in irreversible fibrotic replacement of the pancreatic parenchyma. The hallmark of chronic pancreatitis is its heterogeneous nature in etiology, clinical and pathologic presentation, and treatment. Most patients suffer from a combination of debilitating abdominal pain and progressive pancreatic endocrine and exocrine insufficiency. The result is significantly impaired quality of life secondary to symptoms that often require surgical intervention to improve. Treatment focuses on complications of the disease; no treatment to date has been found to address the underlying cause. This monograph provides insight into our contemporary understanding of chronic pancreatitis pathophysiology, clinical course, diagnosis, and therapy. The major focus is on surgical approaches to various anatomic configurations of the damaged pancreas.

Epidemiology

Chronic pancreatitis is generally felt to be a rare disease; the estimated prevalence in the United States is less than 200,000. Chronic pancreatitis prevalence has remained relatively stable over time, at approximately 35-100 per 100,000 adults.[1-5] The incidence of chronic pancreatitis, on the other hand, appears to be increasing slightly over time (Fig. 1). A general incidence rate of 5 per 100,000 patient years is accepted.[3-6] The majority of patients with chronic pancreatitis are diagnosed in adulthood, but chronic pancreatitis can develop in a small group of juveniles with hereditary predisposition. Men are slightly more prone to developing chronic pancreatitis, possibly because of their increased prominence of risk factors such as cigarette smoking and alcohol use. Despite its relatively low prevalence, chronic pancreatitis is a remarkably costly disease, accounting for more than $150 million of healthcare spending each year in the United States.[6]

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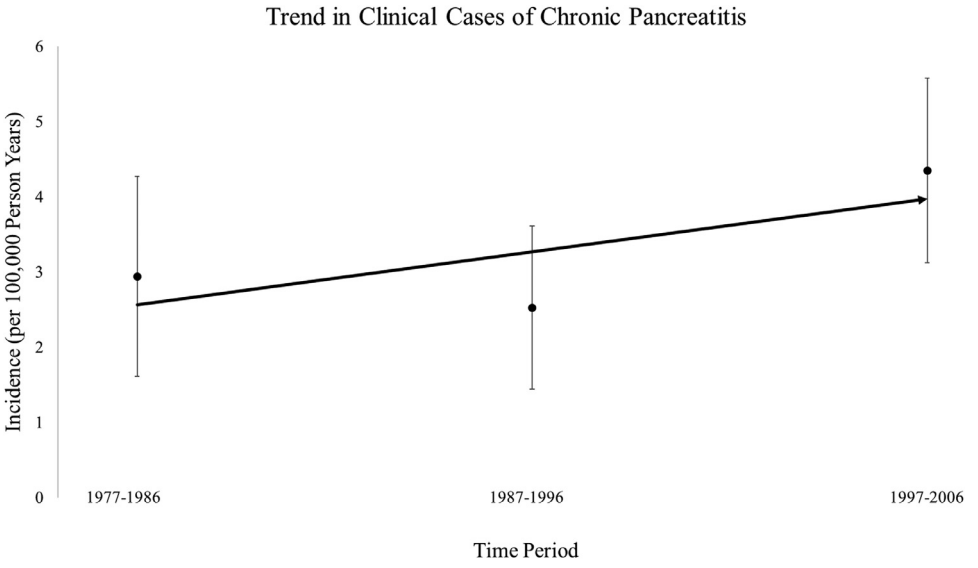

Fig. 1. Trend in clinical cases of chronic pancreatitis. Age and sex adjusted incidence (per 100,000 person years), with 95% confidence intervals, among 3 time periods. Figure created using data published by Yadav and colleagues. [3]

Etiology and pathophysiology

Current understanding of the disease suggests that the etiology of chronic pancreatitis is multifactorial in nature. Risk factors include alcohol, nicotine/tobacco, poor nutrition, pancreatic ductal obstruction, immunologic factors, and metabolic factors[1]. A thorough history for pancreatitis risk factors should be taken. To this end, 2 systems have been helpful: the TIGAR-O and M-MANNHEIM classifications. The TIGAR-O system includes Toxic/metabolic, Idiopathic, Genetic, Autoimmune, Recurrent acute pancreatitis, and Obstructive etiologies. The M-MANNHEIM risk factors include Multiple risk factors, Alcohol consumption, Nicotine consumption, Nutritional factors, Hereditary factors, Efferent duct factors, Immunologic factors, and Miscellaneous and rare metabolic factors. From a practical standpoint, a thorough history of the pancreatitis chronology, other risk factors based on the above systems, as well as family history should be taken. Genetic testing is recommended for patients with unclear etiology, especially in younger patients.[2] Patients with idiopathic chronic pancreatitis should be evaluated for PRSS1, SPINK1, CFTR, and CTRC gene mutations at a minimum; extended panels are available that provide more than a dozen additional gene profiles. Consideration should be given to referral to an experienced genetic counselor. It is quite informative for the clinician to consult directly with the genetic counselor. Importantly, our understanding of genetic profiles and their effect in chronic pancreatitis are evolving rapidly. Currently, perhaps the most practical application involves informing management of the chronic pancreatitis patient being considered for total pancreatectomy with auto-islet transplantation (TP-IAT).

The important hereditary component of chronic pancreatitis continues to be elucidated (Table 1).[3-8] Alcohol and tobacco are the most significant risk factors contributing to chronic pancreatitis and appear to have a synergistic effect in disease development.[9,10] In patients with chronic alcohol use, concurrent use of tobacco is associated with a 5-fold increased risk for chronic pancreatitis development and is associated with earlier development compared to nonsmokers.[9] However, the vast majority of alcohol and tobacco users do not develop chronic pancreatitis, further suggesting an important underlying genetic susceptibility.

Table 1
Genetic mutations associated with chronic pancreatitis and associated mechanisms.

Gene (abbreviation)	Mechanism
Calcium sensing receptor (CaSR)	Defective calcium homeostasis
Cationic trypsinogen gene (PRSS1)	Inappropriate activation of trypsinogen
Chymotrypsin C (CTRC)	Failure to inactivate prematurely activated trypsin
Claudin 2 (CLDN2)	Disease modifier; accelerates transition from recurrent (alcohol-related) acute pancreatitis to chronic pancreatitis
Cystic fibrosis transmembrane conductance regulator (CFTR)	Pancreatic ductal obstruction due to inspissated secretions
Serine protease inhibitor, Kazal type 1 (SPINK1)	Failure to inactivate prematurely activated trypsin

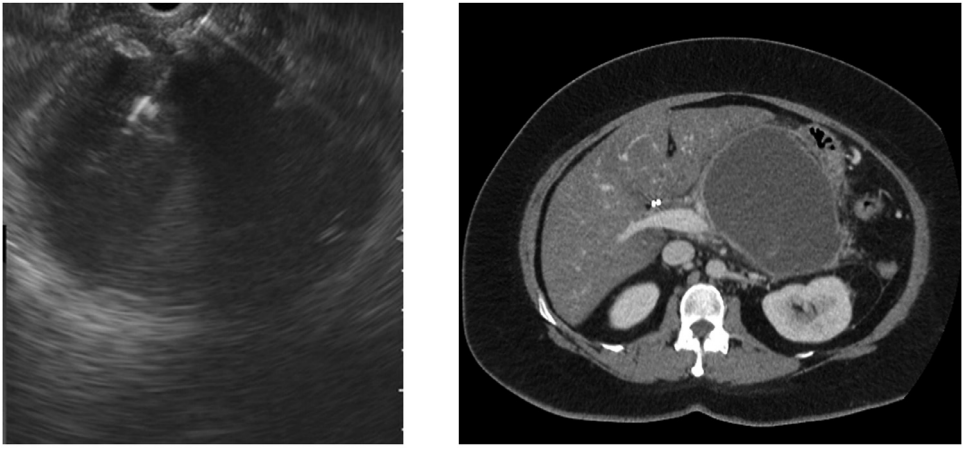

Fig. 2. Pancreatic pseudocyst seen on endoscopic ultrasound (A) and contrast-enhanced CT (B).

Despite improved knowledge of contributing etiologic factors, the underlying disease pathophysiology is poorly understood. In most cases, it seems that a sentinel event results in inappropriate trypsin activation, resultant release of inflammatory mediators and destructive enzymes, and the development of acute pancreatitis.[11] An unfavorable immune response, combined with environmental factors and/or permissive genetics, escalate to recurrent pancreatic injury and inflammation that ultimately results in fibrosis and chronic pancreatitis.[12,13] This spectrum of disease that includes recurrent episodes of clinical or subclinical acute pancreatitis (inflammation) progressing to chronic pancreatitis ultimately places the patient at an increased risk for pancreatic cancer.[14-16] Irrespective of etiology, the end pathologic result is fibrosis, destruction, and chronic inflammation of the pancreas parenchyma causing pain, pseudocyst from pancreatic duct disruption (Fig. 2), and obstruction of local gastrointestinal organs such as the common bile duct and duodenum.

Two less commons subtypes of chronic pancreatitis deserve brief mention: tropical pancreatitis and autoimmune pancreatitis (AIP). Tropical pancreatitis is predominantly seen in Asia, most commonly in southern India.[17] Patients with tropical pancreatitis commonly have SPINK 1 mutations (up to 50%), and typically manifest a rapidly progressive phenotype, with the hallmark of pancreaticolithiasis.[17] A second specific but rare cause of chronic pancreatitis is autoimmune. Understanding of AIP pathophysiology is unfolding slowly; 2 subtypes of AIP have been identified based on their specific histopathologic features.[18] Type 1 AIP, also known as lymphoplasmacytic sclerosing pancreatitis, represents 1 manifestation of a systemic autoimmune

disorder in which multiple organs (including salivary glands, kidney, biliary tree, and retroperitoneal fibrosis) may be affected. Type 1 AIP patients almost always have a circulating IgG4 concentration that is more than 2 times the upper limit of normal. Type 2 AIP, or idiopathic duct-centric pancreatitis, affects younger patients (40-50 years old), who typically present with recurrent acute pancreatitis (RAP). Serum IgG4 is elevated in only 25% of idiopathic duct-centric pancreatitis patients. Histopathology shows dense lymphoplasmacytic infiltration and inflammation prominently affecting periductal regions. Initial treatment of both type 1 and type 2 AIP is with systemic steroid administration.[17,18] Surgical intervention in AIP patients is usually related to mass effect or pancreatic duct stricture concerning for malignancy.

Clinical presentation

The hallmark symptom of chronic pancreatitis is debilitating abdominal pain that significantly impacts a patient's quality of life.[19,20] The pain is characteristically deep, sharp, epigastric abdominal pain radiating to the back (between the scapulae) and is constant and daily with episodes of increased severity. Endocrine failure (type 3C diabetes mellitus) and exocrine failure are common.[21-23] Chronic pancreatitis is the leading cause of type 3c diabetes mellitus and represents an important diagnostic distinction as special therapies are available for patients with diabetes secondary to pancreatic diseases.[24]

A typical clinical presentation involves a patient with a single episode of acute pancreatitis, perhaps of biliary origin, who recovers from the initial episode and remains asymptomatic for a few years. The patient subsequently develops recurrent episodes of acute on chronic pancreatitis (RAP) that at some point pass the diagnostic criteria to chronic pancreatitis. From a practical clinical standpoint, a common clinical story involves increasing frequency and often times increasing severity of the acute pancreatitis flares. Persistent and ineffective management simply by prescribing opioid analgesics is unfortunately far too common in this scenario as the patient may be mislabeled as alcoholic or drug-seeking. Interventions for chronic pancreatitis are most effective early in the disease and once a patient has progressed down a path requiring chronic daily narcotics, it is very difficult to separate pain from the disease from the dependence situation.

Additional symptoms include nausea, vomiting, anorexia, and weight loss. Post-prandial acute exacerbation of these symptoms is fairly common. Physical examination may reveal signs of malnourishment and weight loss. Abdominal pain with palpation may or may not be present. Blood laboratory testing is often unrevealing except in the setting of biliary obstruction, where elevations in alkaline phosphatase and direct (conjugated) bilirubin are seen. The pancreatic cancer tumor marker carbohydrate antigen 19-9 (CA 19-9) may be elevated simply by the inflammatory state (ie., a "false-positive" for pancreatic cancer). The clinician should be mindful that elevations in serum amylase and lipase might not be seen in acute on chronic pancreatitis, as the "burned-out" pancreas will not produce high volumes of these enzymes.

Local complications of chronic pancreatitis include pancreatic pseudocyst, biliary stricture, duodenal stricture, mesenteric vein thrombosis, visceral artery pseudoaneurysm, and pancreatic ductal adenocarcinoma (PDAC) (Fig. 3).

Pancreatic pseudocyst implies, by definition, disruption of the pancreas ductal architecture. Understanding the underlying pancreas duct anatomy is critically important for therapeutic planning. Some pseudocysts may be treated effectively by endoscopic therapy alone, whereas others require surgical intervention and/or resection of diseased parenchyma. Patients with pseudocyst may present with abdominal pain, may have gastrointestinal (GI) symptoms such as nausea and vomiting related to gastric outlet obstruction, or may be completely asymptomatic. Special attention must be given to the patient whose pseudocyst involves the visceral arterial tree (commonly the splenic artery). The pseudocyst is a chronic inflammatory process and can weaken the vascular wall leading to pseudoaneurysm and acute, potentially fatal, intra-abdominal hemorrhage.[25] Vascular hemorrhage into a pseudocyst uniformly leads to sudden acute pain likely from expansion of pseudocyst wall (which in most cases will arrest the acute

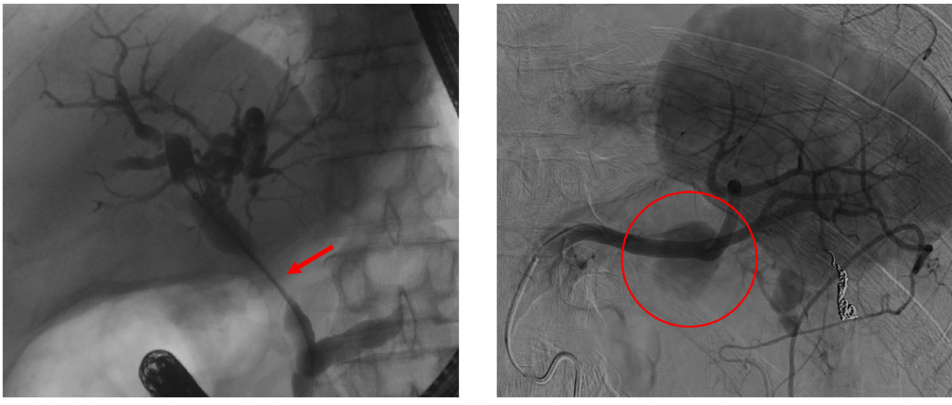

Fig. 3. Sequelae of chronic pancreatitis. (A), Biliary stricture (arrow) and (B), splenic artery pseudoaneurysm (circle) secondary to chronic inflammation from chronic pancreatitis.

Table 2
Indications for intervention in chronic pancreatitis.

Intractable pain
Pancreatic pseudocyst (symptomatic)
Pancreatic duct stricture/obstruction
Biliary stricture
Duodenal stricture
Visceral artery pseudoaneurysm
Gastric varices with hemorrhage
Pancreatic mass/adenocarcinoma

hemorrhage). Ruptured hemorrhagic pseudocyst is uncommon but should be considered a true surgical emergency. The diagnosis of visceral arterial pseudoaneurysm should prompt urgent treatment by interventional radiology techniques as a first line.

Patients with biliary stricture related to chronic pancreatitis may be asymptomatic or may present with pain as well. Liver chemistry analysis should be part of routine periodic clinical evaluation with patients with chronic pancreatitis. Alkaline phosphatase is an early harbinger of biliary obstruction and is often elevated well before bilirubin.[26] Patients with overt clinical jaundice may be decompressed endoscopically; however, intra-pancreatic common bile duct strictures are notoriously difficult to treat durably with endoscopic therapy alone.[26]

Duodenal stricture, similar to biliary stricture, may be diagnosed early, with minimal symptoms, or may present overt gastrointestinal symptoms of nausea and vomiting. A detailed clinical history should be taken from the patient regarding appetite, early satiety, nausea, and vomiting as symptoms of early duodenal stricture may be insidious. The presence of duodenal involvement obviously affects the choice of operation.

Pain represents the most common indication for operative intervention; however, other local complications (Table 2) and concern for malignancy are also clear operative indications.[27,28]

Patients with chronic pancreatitis have at least a 3-fold increased risk of developing PDAC, with select studies reporting risk ratios as high as 16-fold.[29-31] After 20 years of a chronic pancreatitis diagnosis, as many as 5% of patients will develop pancreatic cancer.[30,32] Most cases of PDAC associated with chronic pancreatitis are diagnosed within the first 5 years after chronic pancreatitis diagnosis; however, the underlying chronic pancreatitis likely has gone undetected for some time. The associated long-standing persistent pancreatic inflammation promotes neo-

plastic transformation by interrupting normal cellular homeostasis.[33] With surgical drainage, this inflammatory process is diminished or even halted, and the increased risk of pancreatic cancer is mitigated in chronic pancreatitis patients undergoing operative intervention.[34,35] Early diagnosis of pancreatic cancer is extremely difficult in chronic pancreatitis patients[36]; however, survival outcomes after resection do not appear to be different from those in pancreatic cancer patients without chronic pancreatitis.[37]

Diagnosis

The ability to diagnose chronic pancreatitis is often dependent on the phase of the disease. In early chronic pancreatitis, changes may be subtle and frequently go unnoticed. Diagnosis of late chronic pancreatitis is more obvious, as radiographic changes of the pancreas become clear. Cross-sectional imaging, including computed tomography (CT) or magnetic resonance cholangiopancreatography, may suggest chronic pancreatitis with findings such as pancreatic parenchymal fibrosis, atrophy, and/or edema, pancreatic ductal dilation, and parenchymal and/or ductal calcifications (Fig. 4).[38]

The diagnosis of chronic pancreatitis is practically challenging for several reasons. No gold standard exists among available imaging studies; instead, the gold standard for the diagnosis of chronic pancreatitis is histology. However, pancreatic tissue is not commonly sampled due to concerns for invasive biopsy complications. In addition, early chronic pancreatitis is not visualized easily with current cross-sectional imaging techniques. The duct and parenchymal changes seen in later stage disease on imaging studies serve as a surrogate for tissue biopsy.

A detailed clinical evaluation may be the best diagnostic modality in chronic pancreatitis. Evaluation should involve careful interrogation for the patient's pain quality, character, and history including prior episodes of acute pancreatitis. Risk factors for exposure and family history should be sought. A history of maldigestion may suggest early exocrine insufficiency. In the setting of the patient who is thought to have chronic pancreatitis the next step is cross-sectional imaging.

Either CT scan or magnetic resonance imaging (MRI) of the abdomen are recommended as first line imaging studies. Again, the caveat is that early pancreatitis anatomic changes will not manifest easily identifiable radiologic changes. The best data comparing various imaging modalities suggest that sensitivity and specificity of CT, MRI and endoscopic ultrasound (EUS) are similar: sensitivity, MRI 78%, CT 75%, and EUS 81%; specificity MRI 96%, CT 91%, and EUS 90%.[39] These data were accrued from a systematic review and meta-analysis of nearly 3,500 patients. Clinicians are generally familiar with both CT and MRI, so either test serves as a reasonable first line imaging study.

Secretin enhanced MRI is an important adjunct and serves as the next line of visualization. This test may permit improved visualization of pancreas duct anatomy but also allows quantification of pancreas secretory function, giving insight to the severity of functional disease progression. Secretin enhanced magnetic resonance cholangiopancreatography is a relatively expensive test and therefore its role currently is as a secondary test. Pancreatic function testing, although important in the diagnosis of exocrine pancreas insufficiency, plays a complimentary role in the diagnosis of chronic pancreatitis itself. (Fig. 4).[40]

Endoscopic retrograde cholangiopancreatography (ERCP) allows for detailed evaluation of pancreatic ductal anatomy, identifying features of chronic pancreatitis such as intraductal filling defects, main duct dilation, side branch dilation, and irregular duct contour (Fig. 4).[41,42] Although ERCP is an invasive procedure, it also offers therapeutic benefit.

EUS provides detailed evaluation of the pancreatic parenchymal and ductal anatomy and may assist diagnosis in patients with early chronic pancreatitis and the absence of characteristic findings on less invasive imaging (Fig. 4).[43] EUS, however, is highly operator specific. Benefits and drawbacks of each imaging modality are summarized in Table 3.

The gold standard for diagnosis of chronic pancreatitis is histologic evaluation of pancreas tissue most commonly obtained by EUS guided fine-needle aspiration (FNA) biopsy. It should

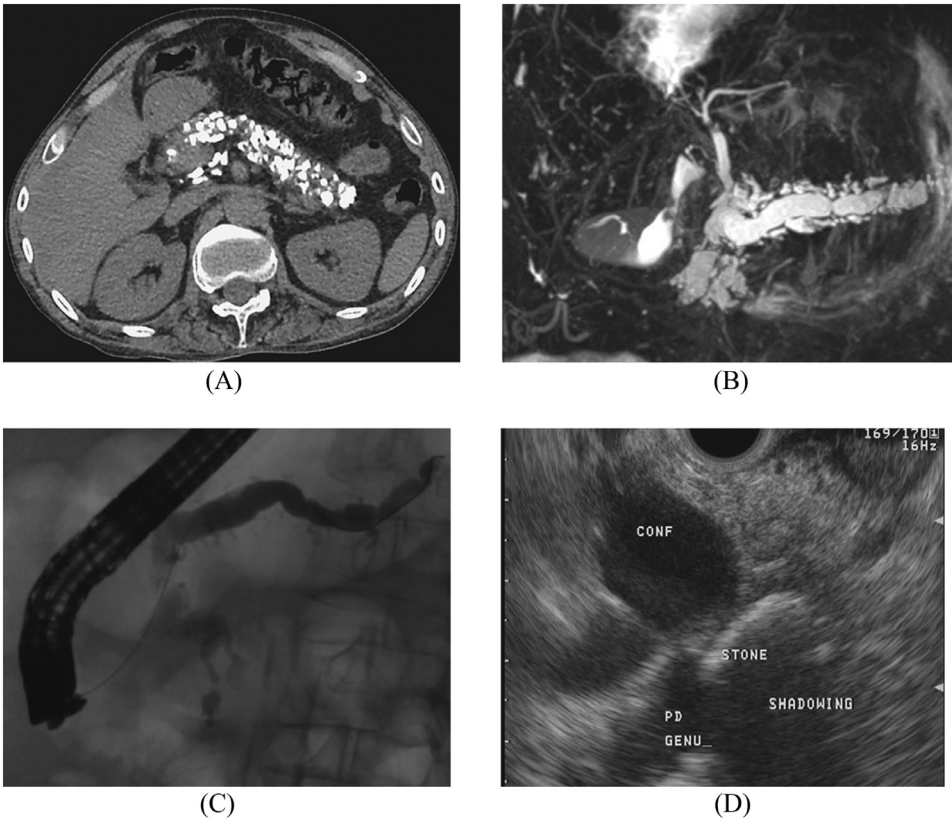

Fig. 4. Diagnostic imaging and characteristic findings in chronic pancreatitis. (A), CT with significant pancreatic parenchymal calcification and atrophy. (B), Secretin-enhanced magnetic resonance cholangiopancreatography (MRCP) demonstrating dilation of the main pancreatic duct with dilated and ectatic side-branches. (C), ERCP displaying dilation of the main pancreatic duct, side-branch irregularities, and irregular duct contour (Cambridge grade V). (D), Endoscopic ultrasound demonstrating detailed view of pancreatic duct anatomy. PD GENU, pancreas neck; STONE, stone in main pancreatic duct with posterior acoustic shadowing.

be considered that histologic fine-needle aspiration (FNA) evaluation may be limited by sample error or patchy inflammation. Currently histologic biopsy of the pancreas is last in the line of diagnostic testing for chronic pancreatitis.

Novel diagnostics are being developed that attempt to diagnose chronic pancreatitis by testing peripheral blood samples[44]. Early and accurate diagnosis of chronic pancreatitis may allow for disease intervention that can minimize the risk of progression to disease specific complications.

Medical management

Patients with significant anatomical obstruction as evidenced by a dilated main pancreatic duct are typically managed by medical therapy or surgical drainage. Medical therapy for chronic pancreatitis patients is commonly reserved for patients without evidence of ductal obstruction ("small duct" disease) or those with modest pain symptoms. Initial treatment of chronic pancreatitis aims to address symptoms and improve quality of life. Patients are counseled for alcohol and tobacco cessation. These lifestyle changes alone can dramatically improve pain.[45,46] First

Table 3
Pros and cons of diagnostic modalities in chronic pancreatitis.

Modality	Pros	Cons
CT	• Reproducible • Relatively inexpensive • Calcifications easily identified • Specific in severe disease	• Limited duct evaluation • Poor sensitivity • Nephrotoxic contrast • Ionizing radiation
MRCP	• Detailed duct anatomy • Detailed parenchyma anatomy • Noninvasive • Secretin provides functional information • No ionizing radiation	• Relatively expensive • May miss subtle changes in duct side branches • May miss small calcifications • Contraindicated in patients with ferromagnetic implants
ERCP	• Detailed duct anatomy • Potential for therapeutic intervention	• Invasive • Requires sedation/general anesthetic • Risk of acute pancreatitis, hemorrhage, or perforation
EUS	• Excellent duct anatomy detail • Excellent parenchyma detail • Sensitive even in early disease • Offers (limited) therapeutic intervention	• Invasive • Requires sedation • Operator dependent • Small risk of perforation

Abbreviations: CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangipancreatography.

line pain control strategies aim to avoid opioid prescriptions, but patients often progress to requiring opioids.[47] Interventions, such as an intrathecal pain pump or celiac plexus neurolysis are effective in select patients.[48,49]

A number of antioxidants have been studied for the treatment of chronic pancreatitis pain. These antioxidants include vitamin A, C, E, selenium, and methionine. The goal of antioxidant treatment is to decrease ischemia and thereby ischemic induced inflammation and stimulus of peri-pancreatic nerves. Prospective randomized studies of antioxidants have produced mixed results.[50] Current guidelines suggest that antioxidant therapy is reasonable, although benefit in terms of pain reduction is likely modest.[2]

Nutritional optimization often requires pancreatic enzyme replacement and commonly supplemental enteral nutrition via tube feeds.[51] The risk of malnutrition secondary to pancreatic exocrine insufficiency is often amplified by sociopsychological factors and food avoidance resulting from abdominal pain. The presence of malnutrition from pancreatic exocrine insufficiency is associated with poor quality of life and increased mortality in chronic pancreatitis.[52,53] Effective nutritional support requires counseling on healthy eating habits and positive lifestyle choices in addition to nutritional supplementation and food fortification.

Treatment of pancreatogenic diabetes mellitus (type 3c) requires lifestyle modifications and anti-hyperglycemic agents.[54] The diagnosis of pancreatogenic diabetes mellitus can be difficult and may coexist with type 1 or (more commonly) type 2 diabetes mellitus. Increasing recognition and understanding of type 3c diabetes mellitus has resulted in improved recommendations to help guide the physician in management.[55] Decreased insulin secretion, decreased pancreatic polypeptide response, hepatic and peripheral insulin resistance, and maldigestion of nutrients from pancreatic exocrine insufficiency (and the associated effect on incretin hormone response) contribute to the complexity in managing diabetes mellitus in chronic pancreatitis patients.[56]

The approach to pain in chronic pancreatitis typically follows a stepwise approach as recommended by the World Health Organization[2]. This stepwise approach begins with non-steroidal antiinflammatory drugs, followed by low potency opioids, followed by longer acting opioids. Celiac plexus blockade (CPB) is applied commonly in clinical practice. The evidence supporting use of CPB is low quality. In practice, approximately 50% of patients respond to CPB and those who do respond have a very short response. In some cases, however, CPB may be useful to

help patients through a particularly difficult pain episode. Pancreatic enzyme supplementation is typically not recommended as a specific treatment to improve pain.

Endoscopic interventions are the first line in addressing pain and physical manifestations of chronic pancreatitis, including pancreatic duct stricture, lithiasis, and pseudocyst.[57] Endoscopic intervention may include stricture dilation and stenting, extracorporeal shock wave lithotripsy with endoscopic removal of stones, and/or transpapillary or transmural pseudocyst drainage.[58] Several prospective studies have suggested that early surgical intervention yields superior results in chronic pancreatitis.[59-62] Any intervention, endoscopic or surgical, must be considered in the setting of multidisciplinary evaluation.

Operative management

History of surgery for chronic pancreatitis

Some of the first surgical interventions for chronic pancreatitis involved resection of pancreatic tail. During this time, the 1950s, surgeons were reluctant to operate on the pancreatic head due to the complex adjacent anatomy. The first drainage procedure (DuVal) involved resection of pancreatic tail with splenectomy followed by pancreatecticojejunostomy. The hope was that retrograde drainage would improve pain. Drainage procedures progressed due to the efforts of Charles Puestow and his contemporaries in Chicago (most notably Partington and Rochelle) who performed lateral pancreatecticojejuonstomy. At the same time, enthusiasm for extended distal pancreatectomy grew to the point where 95% pancreatectomy, the so called “Child procedure”, came to favor. Close follow-up by Child and his colleagues revealed that extended pancreatectomy was accompanied by poor outcomes due to metabolic and nutritional problems and the 95% pancreatectomy has subsequently been abandoned.

In the 1970s and 1980s experience grew with pancreatic head resection, and PD was applied to the chronic pancreatitis patients. The prevailing theory of the time was that the “pacemaker” of pain in chronic pancreatitis was located in the pancreatic head. This theory was promulgated by Dr. William Longmire in California. Introduction of various duodenal-preserving pancreatic head resections (DPPHR) by Beger, Frey, and others in the 1980s expanded surgical intervention for chronic pancreatitis patients mostly with large duct disease (although Izbicki notably applied his drainage procedure to those with small duct disease). The goals of these DPPHR were to preserve parenchyma and hormonal function while providing adequate drainage of the pancreas.

In the mid 1970s, the University of Minnesota group first introduced total pancreatectomy with replacement of the isolated islets by transplantation (TP-IAT) to the liver. Subsequently, TP-IAT has been embraced as standard therapy for highly select chronic pancreatitis patients with small duct disease and specific genetic abnormality. A broad range of operative interventions are available to treat patients with chronic pancreatitis. The informed surgeon must be skilled in not only the technical application of these procedures but also accurate interpretation of the anatomy suitable for each specific procedure. Truly one size operation does not fit all patients in this remarkably heterogeneous disease process.

Indications and preoperative considerations

A variety of indications exist for operative intervention in chronic pancreatitis (Table 2). The most common indication is debilitating pain refractory to medical and endoscopic treatment.[27,28] The surgeon must consider the unique clinical picture of each patient to provide the best recommendation for surgical intervention. Prior to operation, patients should be nutritionally optimized and counseled on the importance of smoking and alcohol cessation.[45,46,51] If splenectomy is indicated, vaccinations against encapsulated organisms should be administered preoperatively.[63] Any operative intervention should be delayed in the event of acute pancreatitis flare.

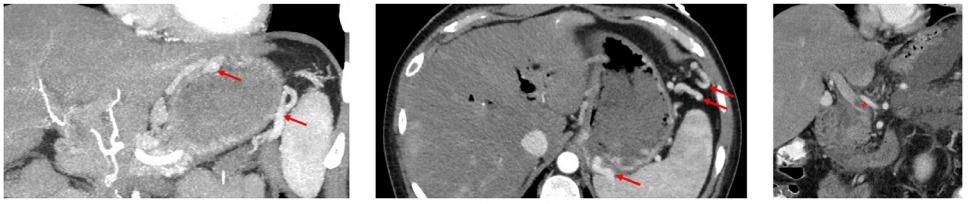

Fig. 5. Splanchnic vein thrombosis in chronic pancreatitis. (A and B, arrow) Splenic vein thrombosis resulting in sinistral (left-sided) portal hypertension with large gastric varices; (C, asterisk) near-occlusive thrombus within the portal vein.

The predominant goals of operative management focus on preserving pancreatic parenchyma, minimizing morbidity, durably relieving symptoms, and improving quality of life. To achieve these goals, appropriate operative selection is critical. Specific considerations include pancreatic parenchymal and ductal anatomy, surrounding anatomy, symptoms, quality of life, and genetics. Technical considerations of surrounding anatomy include the presence of bile duct or duodenum involvement, concern for malignancy, and the presence of portal hypertension. The surgeon must be prepared with "back-up" operative plans based on intraoperative findings.

Sinistral (left-sided) portal hypertension is common in patients with chronic pancreatitis and is frequently seen with pancreatitis-induced splenic vein thrombosis (Fig 5).[64] Portal hypertension secondary to hepatic cirrhosis is less common but must be considered given the association of alcohol with chronic pancreatitis and cirrhosis.[46,65] The prevalence of portal vein thrombosis or superior mesenteric vein thrombosis in chronic pancreatitis patients ranges from 1% to 4% (Fig. 5).[66]

Although the anatomical changes in chronic pancreatitis are heterogenous, a few general guidelines inform operative decision-making.[58] The pancreatic ductal anatomy is the primary component in selecting a suitable operation. Patients with pancreatic ductal dilation will benefit from a drainage procedure, given the presumed ductal obstruction. In patients without pancreatic ductal dilation ("small duct disease"), resection of the inflamed and atrophic pancreas is necessary. In patients with small duct disease, directed resection, if possible, is ideal; however, diffuse pancreas involvement in the setting of small duct disease is a situation potentially best treated with TP-IAT. Additionally, specific genetic components of chronic pancreatitis should lead the clinician to consider TP-IAT as a primary therapy (discussed below).

Exposure of the pancreas

Prior to any mobilization, intraoperative ultrasound is performed using the stomach as an acoustic window. Particular note is made of stone and stricture location, as well as vascular relationships. The gastrocolic ligament should be opened widely to provide satisfactory exposure of the pancreatic body and tail. If vessel-sacrificing spleen-preserving distal pancreatectomy (i.e, "Warshaw" type operation) is anticipated, the surgeon must preserve enough short gastric vessels to permit splenic perfusion. Operation on the pancreatic head usually demands ligation of the anterior pancreaticoduodenal arcades cranially and caudally. The gastroepiploic arterial course is variable; often this vessel is sacrificed at its origin. A wide Kocher maneuver provides safe exposure and manual ventral elevation of the pancreatic head is a useful move with which to control venous hemorrhage from the superior mesenteric or portal veins.

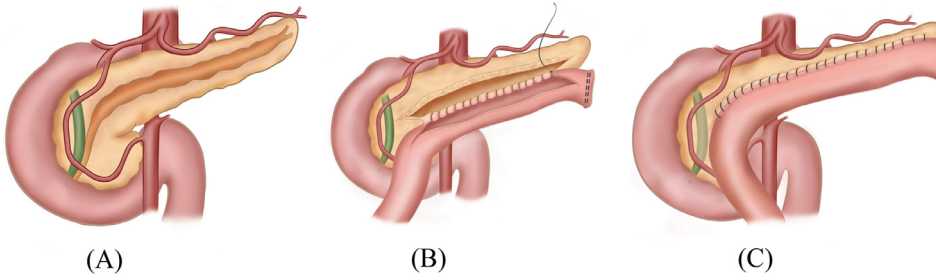

Fig. 6. Lateral pancreaticojejunostomy (LPJ). (A), Typical anatomy ideal for LPJ; (B, C) Relationship of the splenic artery and anterior pancreaticoduodenal arcade to LPJ anastomosis.

Pancreatic drainage

Indications for lateral pancreaticojejunostomy (LPJ) include patients with a diffusely dilated (>7 mm) pancreatic duct with minimal involvement of the pancreatic head (Fig. 6).[28,58,67] The pancreatic duct is usually obvious but may be identified with intraoperative ultrasound or by aspiration with a medium gauge needle. The pancreatic duct is opened along its length into the head, dividing the pancreaticoduodenal artery, as necessary. Pancreatic duct lithiasis is cleared. A Roux-en-Y (R-Y) limb of jejunum is brought through the transverse mesocolon to the left of the middle colic vessels, and pancreaticojejunostomy is performed, usually in 2 layers. At the cranial border of this anastomosis, the surgeon must take care to avoid injury of the splenic artery; at the caudal anastomosis, care is taken to avoid damaging the superior mesenteric vein at the pancreatic neck and the anterior pancreaticoduodenal arcade (Fig. 6). Morbidity after LPJ occurs in 15% to 25% of patients.[68-70] Postoperative pancreatic fistula (POPF) is uncommon; intraabdominal abscess and extrapancreatic infection are more frequent. The potentially life-threatening problem of visceral arterial pseudoaneurysm is rare; it is important to recognize that this complication presents with lower gastrointestinal bleeding in LPJ patients. Postoperative visceral arterial pseudoaneurysm after pancreatic surgery is best managed with endovascular angioembolization or stenting, rather than repeat laparotomy.[71,72] Durable pain relief can be achieved with LPJ in up to 90% of properly selected patients.[69,73,74] Main pancreatic duct decompression with LPJ can delay the progression of endocrine and exocrine insufficiency in chronic pancreatitis patients.[67] Advantages of LPJ include pancreatic parenchymal and splenic preservation; however, untreated disease in the head of the pancreas can result in recurrent pain.[75,76] Combining pancreatic head resection with LPJ can increase the likelihood of symptom relief and is discussed in detail in the subsequent section.

Pancreatic resection

Directed pancreatic resection is useful in patients with disease confined to only a portion of the pancreas. Chronic pancreatitis patients with disease predominantly localized to the body and tail of the pancreas, or with a pancreatic duct stricture in this area, may benefit from distal pancreatectomy (DP) (Fig 7).[27,28] Given the chronic inflammatory process in the left upper quadrant, splenic preservation is not often possible[77]. Intraoperative ultrasound of the pancreatic duct and pancreatic parenchyma can guide decision-making regarding the extent of pancreatic resection. Postoperative morbidity is experienced in 15% to 30% of patients undergoing DP, with the predominant cause of morbidity being intraabdominal abscess or complications from existing patient comorbidities.[78-80] Long-term improvements in pain are seen in up to 80% to 90% of properly selected patients.[79,81] Often a significant resection of the pancreatic body and tail is required resulting in rates of new-onset diabetes mellitus ranging from 20%

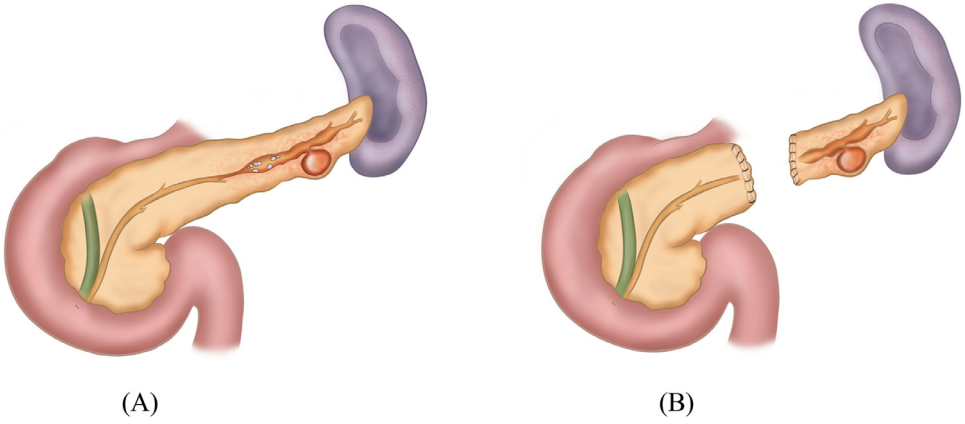

Fig. 7. Distal pancreatectomy (DP). (A) Pancreatic duct dilation, lithiasis, and communication pseudocyst isolated to the pancreatic tail, (B), Resection of only the involved gland.

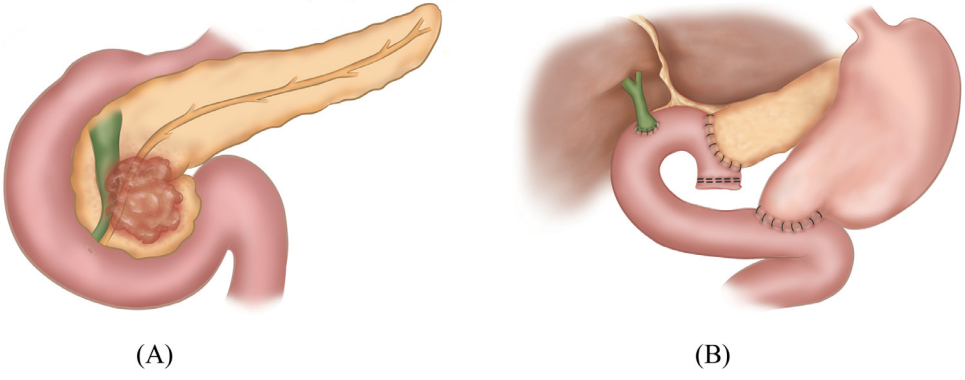

Fig. 8. Pancreatoduodenectomy (PD). (A), Small duct disease with an inflammatory mass in the head of the pancreas with associated biliary dilation, (B), Reconstruction after completion of PD.

to 51% after DP for chronic pancreatitis.[82] Pancreatic exocrine function appears to remain stable after DP.[69,83]

When performing DP, early control of the splenic artery is ideal, although not always possible technically from the anterior approach. The setting of splenic vein thrombosis with sinistral portal hypertension presents a unique technical challenge and splenic preservation is exceptionally difficult in this situation. Preoperative splenic artery embolization is intuitively attractive as a means of decompressing collateral venous flow; however, in practice this strategy has not proven to be particularly useful. Routine intraperitoneal drainage of the operative bed after DP remains a topic of controversy. Several institutional experiences have reported mixed results and a recent meta-analysis of 10 trials reported similar outcomes with and without routine intraperitoneal drainage.[84]

Directed resection of the pancreatic head with pancreatoduodenectomy (PD) is utilized in patients with small duct disease involving the head of the pancreas and causing biliary or duodenal stricture, and/or a concern for malignancy (Fig 8).[28,58] Surgeons operating on patients with chronic pancreatitis must respect the substantially increased risk of PDAC occurring in this population.[29-32] This awareness is particularly important when considering drainage or partial

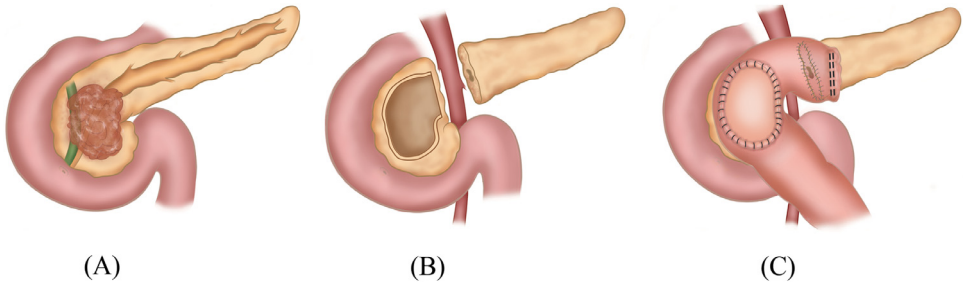

Fig. 9. Beger's duodenum-preserving pancreatic head resection. (A), Bulky disease in the pancreatic head, (B), Transection of the pancreatic neck allows deep coring out of the pancreatic head, (C), The cored pancreas head and remnant distal pancreas are anastomosed to a Roux-en-Y limb of jejunum.

pancreatectomy (ie, duodenum-preserving pancreatic head resection, discussed below). The diagnosis of PDAC is remarkably difficult in chronic pancreatitis patients; the pancreatic anatomy is drastically distorted by scar and calcium, which significantly decreases the accuracy of imaging studies[36,85,86] The tumor marker carbohydrate antigen (CA) 19-9 may be elevated simply from the inflammatory response of chronic pancreatitis, or spuriously elevated in the setting of jaundice from biliary obstruction.[85,86] It is worth noting that up to 10% of the population (Lewis blood type antigen A negative) will not make CA 19-9[86]. Attention to clinical clues such as weight loss or suspicious pancreatic duct stricture should prompt clinicians to consider resection as opposed to drainage procedures.

In properly selected patients, PD provides pain relief in up to 80% to 90% of patients; however, this operation carries significant morbidity, ranging from 30% to 50% and mortality rates from 1% to 5%, making PD the most morbid of procedures for chronic pancreatitis.[87-90] Despite the increased perioperative morbidity, long-term quality of life and pain relief provided by PD is similar to duodenum-preserving pancreatic head resection. During long-term follow-up after PD, new-onset diabetes mellitus develops in approximately 25% of patients and new onset exocrine insufficiency in approximately 50% to 75% of patients.[91-93]

Duodenum-preserving pancreatic head resection

Duodenum-preserving pancreatic head resection (DPPHR) techniques were developed with the goal of improving safety and quality of life by sparing peripancreatic structures. First published in the 1980s, Beger described a method of DPPHR with mortality rates of less than 2%.[94,95] Several variations of this theme have subsequently been described, including the Berne,[96] Frey,[97] and Izbicki[98] modifications.

Patients with bulky disease in the pancreatic head with or without pancreatic duct dilation in the tail are candidates for Beger's operation (Fig. 9).[28,58] The key feature of this operation involves transecting the pancreatic neck, which permits deep coring out of the pancreatic head. This excavation leaves behind a rim of pancreatic tissue around the duodenal sweep. Both the cored pancreas head and remnant body/tail are anastomosed to a R-Y limb of jejunum.[94,95] The surgeon must be mindful of the portal and superior mesenteric veins, which are friable in the setting of dense inflammation and may be injured during pancreatic neck transection. The upstream pancreatic tail is drained via the same limb of jejunum by way of end-to-side pancreaticojejunostomy. In experienced hands, postoperative morbidity and mortality of Beger's operation are 25% and 1%, respectively.[89,95,99] Long-term success in terms of pain relief, endocrine insufficiency, and exocrine insufficiency is similar to that seen in PD and other DPPHR.[89]

The Berne modification of DPPHR is useful in patients with bulky pancreatic head disease with or without pancreatic duct dilation in the tail (Fig. 10).[28,58,96] The main difference between the Berne modification and the Beger procedure is that the Berne leaves the neck of the

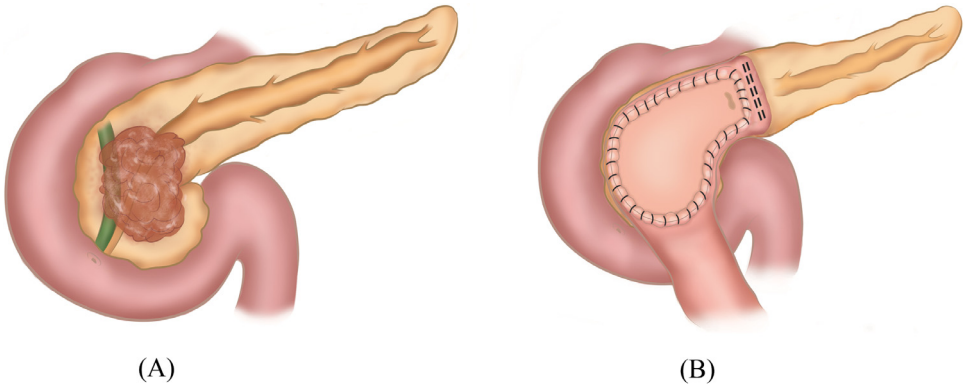

Fig. 10. The Berne modification of duodenum-preserving pancreatic head resection. (A), Bulky disease in the pancreatic head, (B), The pancreatic neck is left intact to avoid potential injury to the portal vein during dissection of the pancreatic neck.

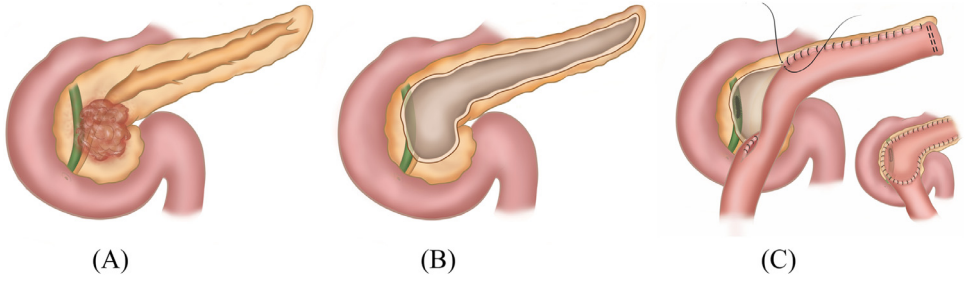

Fig. 11. Frey's duodenum-preserving pancreatic head resection. (A), Pancreatic duct dilation throughout the neck, body, and tail of the pancreas with bulky disease in the pancreatic head, (B), Coring of the pancreatic head is combined with pancreatic ductotomy through the neck, body, and tail, (C), Anastomosis of the cored pancreas head and lateral pancreaticojejunostomy are performed using a single Roux-en-Y limb of jejunum. The common bile duct may be opened in the pancreatic head to relieve distal obstruction and achieve drainage (C, inset).

pancreas intact, thereby avoiding potential injury to the portal vein during dissection behind the pancreatic neck (Fig. 10).[96] Additionally, only a single pancreatic anastomosis is performed, as a Roux limb of jejunum is anastomosed to the cored out pancreatic head. Pain relief, morbidity, and mortality rates are comparable to most operations for chronic pancreatitis.[89,96]

Patients with a dilated pancreatic duct throughout the neck, body, and tail of the pancreas in addition to head involvement are candidates for a localized pancreatic head resection combined with LPJ (Fig. 11), as initially described by Frey.[28,58,97] The Frey technique achieves drainage through the gland's length provided by a LPJ, while coring out the head aims to minimize recurrent symptoms due to disease within the pancreatic head, a potential pitfall of LPJ alone (Fig 11).[97] It is notable that Frey's operation does not require division of the pancreas neck. Excellent rates of pain relief, morbidity, and mortality are reported in properly selected patients, again comparable to other types of DPPHR.[75,97,100-104]

The Izbicki modification is less frequently applied but is particularly useful in patients with head dominant disease and a small duct throughout the remainder of the gland (Fig. 12).[98] The Izbicki procedure combines coring out of the pancreatic head with a "V-shaped" coring along the length of the pancreatic duct. Drainage is then achieved via a Roux limb of jejunum anastomosed along the length of the remaining pancreatic parenchyma (Fig. 12), similar to Frey's procedure.

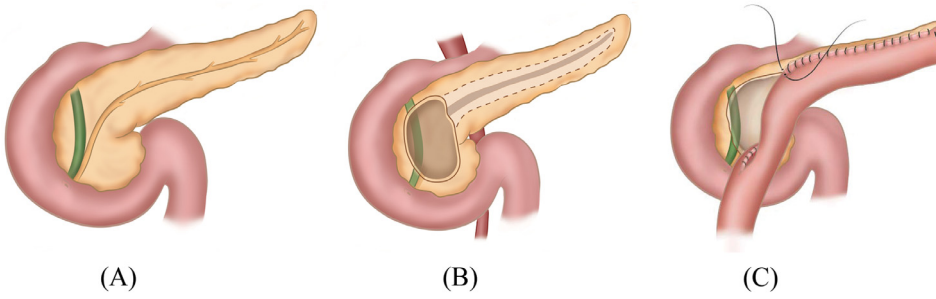

Fig. 12. Izbicki's duodenum-preserving pancreatic head resection. (A), Head dominant disease with a small pancreatic duct throughout the remaining gland, (B), Coring of the pancreatic head is combined with a "V-shaped" coring along the length of the pancreatic duct; (C), Anastomosis is performed similar to Frey's procedure.

Small prospective randomized trials and several retrospective series have compared PD to various modifications of DPPHR, and the various DPPHR techniques among themselves.[90,99-108] The general takeaway message is that these operations are all safe when performed by experienced pancreatic surgeons, and all provide good pain relief to carefully selected patients. Additionally, the rates of new-onset diabetes and/or exocrine insufficiency are similar among the different types of DPPHR and when comparing DPPHR to PD.

Total pancreatectomy with islet cell autotransplantation (TP-IAT)

Chronic pancreatitis patients with small duct disease and diffuse gland involvement are a particularly challenging group to treat. Patients with genetic components of chronic pancreatitis may benefit most from total pancreatectomy,[109] as limited resection or drainage procedures do not halt disease progression in the remaining pancreas. Pancreatic head resection (PD) outcomes were mixed to poor in terms of pain relief. As operative experience with chronic pancreatitis accrued, the concept of total pancreatectomy to treat pain emerged. However, early attempts to treat chronic pancreatitis with total pancreatectomy were met with significant morbidity and mortality. Postoperatively, patients were crippled with extremely brittle type 3c diabetes mellitus; perhaps more importantly was the loss of counteracting glucagon which resulted in hypoglycemic unawareness and life-threatening hypoglycemic events.[110]

In 1977, the Minnesota group reported their experience with total pancreatectomy and islet cell autotransplantation (TP-IAT).[111] Since that time, TP-IAT has become an accepted means of treatment for select patients with small duct chronic pancreatitis (Fig. 13), including patients with hereditary etiology. The last 2 decades have seen a significant increase in utilization of TP-IAT, with promising outcomes in high-volume centers. Short-term pain relief is reported in 80% to 90% of highly select patients.[109,112-116] Insulin independence has been reported to be as high as 20% to 40% in the short-term follow-up.[109,112-117] Not surprisingly, in longer-term follow-up, most will require insulin replacement. After TP-IAT, nearly all patients will require exocrine enzyme replacement. The long-term outcomes after TP-IAT are just beginning to emerge. Morbidity (10%-40%) and mortality (1%-2%) is acceptable and similar to that of PD.[109,112,113,115,116] Long-term pain relief is reported in 50% to 90%.[109,112-114,116] Perioperative outcomes have improved with increasing experience; the publication of consensus criteria will help to guide patient selection.[118] An important point revolves around the genetic profile of individual chronic pancreatitis patients. Emerging data suggest that patients harboring certain genetic mutations may be best served with TP-IAT as primary therapy.[113]

Although TP-IAT has become more generally accepted therapy, relatively few high-volume centers exist. The perioperative evaluation is critically important and involves not just the typical

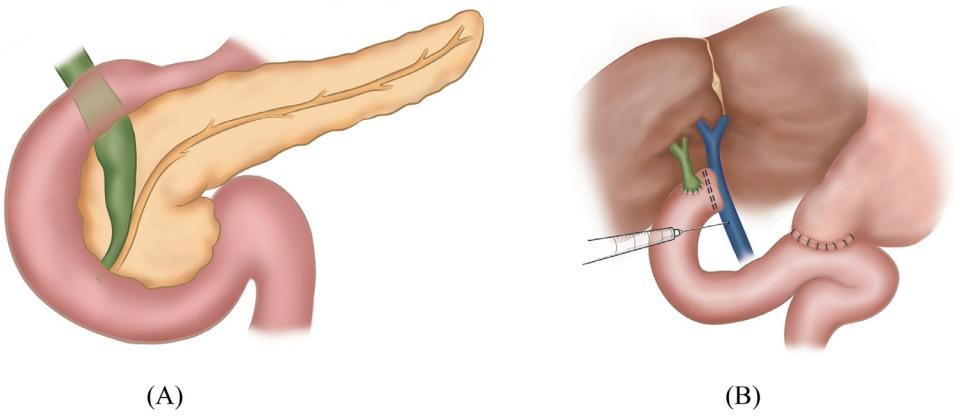

Fig. 13. Total pancreatectomy with islet cell autotransplantation (TP-IAT). (A), Small duct chronic pancreatitis and patients with hereditary etiology of chronic pancreatitis may be candidates for TP-IAT, (B), Islet infusion is performed in the early postoperative period via an interventional radiology procedure cannulating the portal vein.

multidisciplinary team of medical pancreatologists and pancreas surgeons, but also requires significant input from pain specialists, nutritionists, endocrinologists, and geneticists. A functional islet cell isolation team is commonly housed at the treating institution; however, islet preparation off-site with delivery and infusion within a short (<24 hours) postoperative period has been reported with good outcomes.[119] Islet isolation is commonly accomplished by infusing the main pancreatic duct with a collagenase solution.[120] Therefore, the highest yield islet retrieval typically is achieved in patients with normal (native) pancreatic duct anatomy. Patients with prior drainage operations (eg, LPJ) operations and those with prior resection are still candidates for TP-IAT, although the isolation technique is more challenging and islet yield is lower in this setting.[121]

Technically, total pancreatectomy ensues in a fashion similar to PD, without the requirement of pancreatic anastomosis during the reconstruction phase. The vascular supply to the pancreas should be preserved as long as possible, as early ligation of the vessels can lead to islet cell ischemia.[122] Gastro- or duodenojejunostomy and hepaticojejunostomy are performed similar to PD. Islet harvest requires several hours; many centers now infuse the islets into the portal vein via an interventional radiology procedure in the early postoperative period (Fig. 13).[120]

Conclusion

Chronic pancreatitis is a life-altering disease secondary to debilitating pain and significantly impaired quality of life. Its etiology, development, presentation, and treatment are heterogeneous in nature. Medical and endoscopic treatments are useful first line treatment options; however, many chronic pancreatitis patients will require surgery. A surgical approach individualized to the patient is mandatory and must aim to provide durable symptom relief while preserving pancreatic parenchyma and minimizing morbidity. The pancreatic surgeon managing chronic pancreatitis must remain flexible, understanding multiple operative strategies that may be guided by intraoperative findings. With proper patient and operation selection, surgical intervention can provide durable and significant improvements in the symptoms and quality of life of chronic pancreatitis patients.

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