

Systematic Approach to Treatment of Chronic Pancreatitis

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Abstract: Chronic pancreatitis (CP) is a progressive fibroinflammatory disease of the pancreas with complex pathogenesis and diverse etiologies. CP can lead to numerous complications, including pain, exocrine pancreatic insufficiency, and endocrine insufficiency. Although CP is challenging to treat, there are a broad array of treatment strategies, including medical management, endoscopic interventions, and surgery. The goal of this article is to provide a systematic approach to management of CP and an overview of the evidence supporting different therapies.

Chronic pancreatitis (CP) is a disease characterized by progressive inflammation and fibrosis of the pancreas with heterogeneous causes. Irrespective of etiology, CP is challenging to manage. This article outlines a systematic approach to treatment of CP encompassing mitigation of risk modifiers, medical management of CP, and interventional management of CP.

Addressing Risk Modifiers

Once the diagnosis of CP is made, the etiology should be considered. The pathogenesis of CP is complex, and patients may have several contributing risk factors. The TIGAR-O classification system (which stands for toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, and obstructive) identifies and categorizes important risk modifiers for CP.¹ Identifying and addressing underlying CP risk factors may help to slow disease progression.

Alcohol

Heavy alcohol use is an important risk factor for the development of CP,² and patients should be counseled to abstain.³ Alcohol cessation is associated with lower rates of pain, exocrine pancreatic insufficiency (EPI), pseudocysts, recurrent acute pancreatitis (AP), and surgery in CP.⁴ Initial assessment of alcohol use with a validated screening tool (Alcohol Use Disorders Identification Test) to guide multidisciplinary treatment with counseling and pharmacotherapy (naltrexone, acamprosate, and disulfiram) has been shown to be effective in promoting alcohol cessation in CP.⁵

Keywords

Chronic pancreatitis, treatment, guidelines, pancreatic calculi, interventional management, exocrine pancreatic insufficiency

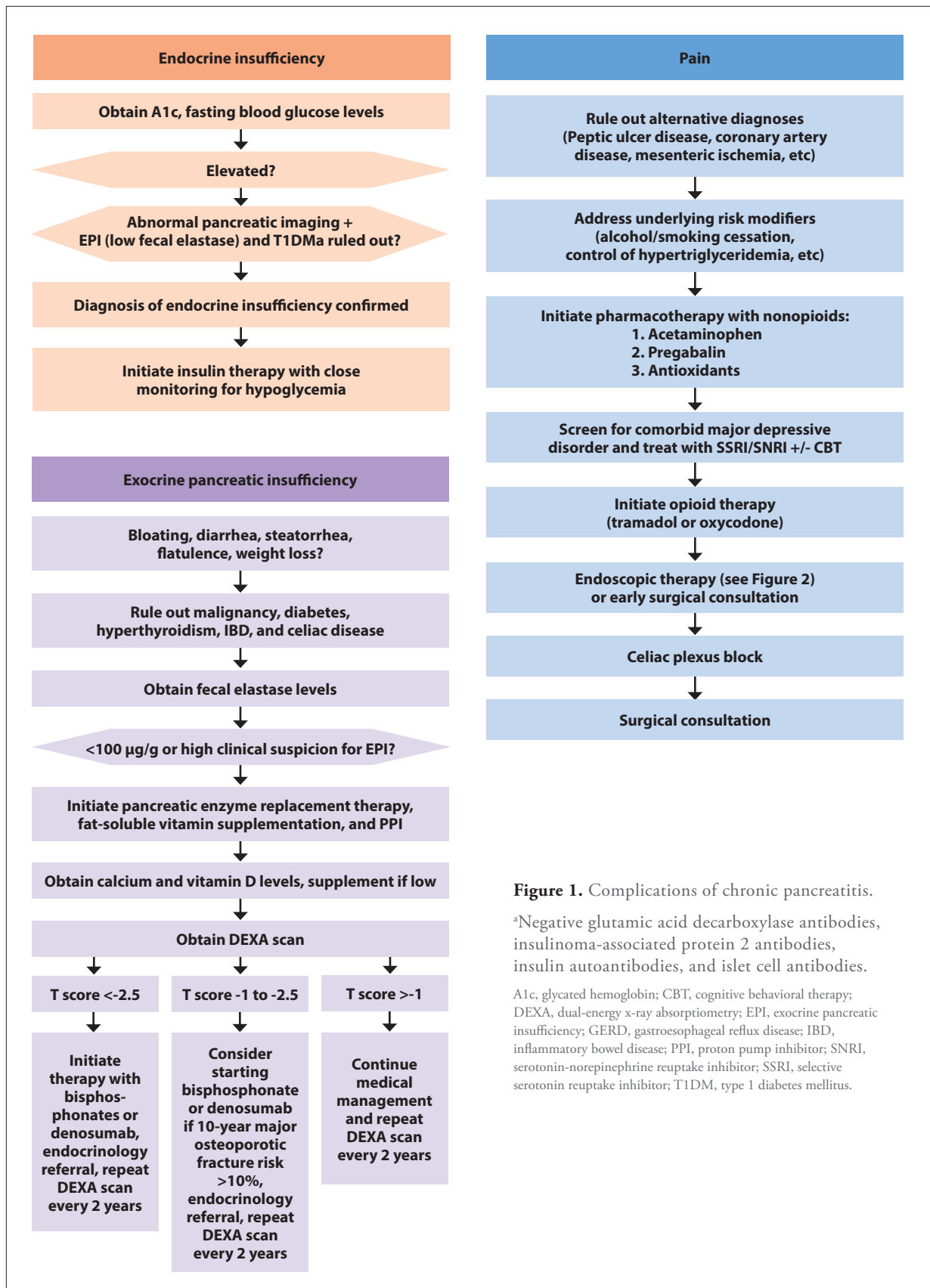


Figure 1. Complications of chronic pancreatitis.

^aNegative glutamic acid decarboxylase antibodies, insulinoma-associated protein 2 antibodies, insulin autoantibodies, and islet cell antibodies.

A1c, glycated hemoglobin; CBT, cognitive behavioral therapy; DEXA, dual-energy x-ray absorptiometry; EPI, exocrine pancreatic insufficiency; GERD, gastroesophageal reflux disease; IBD, inflammatory bowel disease; PPI, proton pump inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; T1DM, type 1 diabetes mellitus.

Smoking

Cigarette smoking is a key risk factor for CP,² and patients should be counseled to stop tobacco use.³ Smoking increases risk of CP complications, including EPI,⁶ pancreatic calcifications,^{6,7} and diabetes.⁷ Total pack-years have a positive correlation with disease severity and pancreatic pseudocyst risk.⁴ Smoking cessation is associated with reduced risk of recurrent AP⁴ but is difficult to achieve. A small cohort study showed counseling and nicotine replacement to be unsuccessful in promoting smoking cessation in CP patients at 18 months.⁸ Prescription of varenicline led to smoking cessation in 19% of patients, and reduced cigarette smoking in a majority at 6-month follow-up in a second cohort of CP patients⁹ and may represent an option worth trying.

Hypertriglyceridemia

Hypertriglyceridemia is a well-established risk factor for pancreatitis,^{1,10} with risk increasing in a dose-dependent manner.¹¹ Hypertriglyceridemia is an important cause of recurrent AP, which in turn can lead to the development of CP.^{1,10} The risk is most pronounced in patients with severe hypertriglyceridemia (15.8% with triglycerides >1771 mg/dL, 3.3% with triglycerides >886 mg/dL).¹² However, in patients hospitalized with hypertriglyceridemia-induced AP, even moderately increased triglyceride levels postdischarge (201-500 mg/dL) confer increased risk of recurrent AP,¹³ which suggests that an aggressive triglyceride goal of less than 200 mg/dL may be appropriate. No studies have compared different triglyceride-lowering therapies for pancreatitis prevention, but options include fibrates, niacin, omega-3 fatty acids, angiopoietin-like 3 inhibitors, and apolipoprotein C-III inhibitors.¹⁴

Medications

As with hypertriglyceridemia, use of certain medications can lead to recurrent AP and an increased risk of developing CP.¹ Upon diagnosis of CP, a patient's medications should be reviewed for drugs that confer an increased risk of pancreatitis. Numerous drugs have been associated with pancreatitis, but supporting evidence is often weak. A recent review article summarized the evidence for drug-induced pancreatitis for 121 medications. Only 3 drugs, azathioprine, 6-mercaptopurine, and didanosine, had strong-quality evidence for causing pancreatitis, 14 drugs had moderate-quality evidence, and 104 drugs had low-quality evidence.¹⁵ If an offending medication is suspected, it should be discontinued or changed to a different drug.

Hereditary Pancreatitis

A number of genetic mutations have been associated with increased risk of development of CP, including *PRSS1*,

CFTR, *CTC*, *SPINK1*, and *CPA1*.¹⁶ A CP diagnosis in young patients with family history of pancreatic disease, diabetes, or hypertriglyceridemia and without obvious risk factors for pancreatitis may suggest a genetic etiology.¹ Referral to a genetic counselor for genetic testing may provide clarity to patients and help guide future treatment decisions.³

Autoimmune Pancreatitis

Autoimmune pancreatitis (AIP) is an immune-mediated fibroinflammatory disease of the pancreas that represents a subset of chronic pancreatitis.¹⁷ There are 2 types of AIP. Type 1 typically presents with painless jaundice and is associated with elevated immunoglobulin G4 (IgG4). Patients may show systemic signs of IgG4-related disease.¹⁸ Type 2 typically presents with painful pancreatitis and is commonly associated with inflammatory bowel disease.¹⁹ Guidelines for diagnosis of AIP rely on imaging findings of the pancreas and pancreatic duct (PD), serology (IgG4 and antinuclear antibody), pancreatic histopathology, and treatment response.²⁰ Endoscopic ultrasound (EUS)-guided fine-needle biopsy may also help confirm AIP and rule out malignancy.²¹ The first-line treatment is prednisone; a typical course is 40 mg daily for 4 weeks with a subsequent taper of 5 mg per week until discontinuation.²² Rituximab has been shown to be effective in patients with relapsing disease.^{22,23} Pancreatic cancer should be ruled out with repeat imaging and carbohydrate antigen 19-9 levels²⁰ 2 weeks after initiation of treatment.²⁴

Other Risk Modifiers

There are numerous other risk modifiers for CP, including hypercalcemia, toxic metals, diabetes and metabolic syndrome, biliary pancreatitis, recurrent and severe AP, obstructive pancreatitis, and infectious pancreatitis.¹

Medical Management of Chronic Pancreatitis

Algorithms outlining a systematic approach for the diagnosis and medical management of CP complications are shown in Figure 1.

Pain

Chronic abdominal pain is one of the most debilitating symptoms of CP. A first step for treatment is acetaminophen, which is safe but frequently inadequate,²⁵ and CP patients achieve lower plasma concentrations than healthy controls.²⁶ Generally, nonsteroidal anti-inflammatory drugs are not recommended in CP owing to their risk of gastrointestinal side effects.²⁷ Opioid medications are effective for treatment of painful CP but carry risks, including addiction, gastrointestinal dysmotility,²⁸ AP, and hyperalgesia.²⁹ Tramadol was found to be more

effective than morphine for treatment of painful CP and conferred lower risk for dysmotility.³⁰ Oxycodone also has been shown to be a superior analgesic to morphine in CP patients.³¹ Treatment of neuropathic pain has demonstrated benefit in CP, with pregabalin significantly reducing pain and improving health status in a placebo-controlled trial.³² Depression and anxiety are highly prevalent in CP patients and are correlated with pain³³; however, no studies exist investigating the use of antidepressants for treatment of painful CP. A retrospective study of CP patients found that several gene loci associated with severe constant pain were in close proximity to or in genes associated with depression.³⁴ Further studies are needed to clarify the role of antidepressants in painful CP. Ketamine infusion has been shown to decrease pressure pain thresholds in CP patients; however, the effect disappeared after the infusion was completed.³⁵ Case series data also showed ketamine to reduce pain in CP patients but did not lead to decreased opioid use.³⁶

The role of pancreatic enzyme replacement therapy (PERT) for treatment of painful CP is controversial, and studies show conflicting results. A Cochrane systematic review and meta-analysis did not show a significant reduction in pain in CP patients treated with PERT.³⁷ However, a large systematic review and meta-analysis of randomized controlled trials (RCTs) consisting of 511 CP patients treated with PERT for EPI did show a significant reduction in abdominal pain as compared with placebo.³⁸ These results suggest that pain relief from PERT in CP patients may be contingent on whether the patient has EPI or not. Nevertheless, given that the existing evidence is equivocal (and many patients with CP have concomitant EPI for which the benefits of PERT are well established) and that PERT is a low-risk intervention, it is not unreasonable to try PERT for pain if cost is not a barrier. The role of octreotide in treatment of painful CP is also controversial with one crossover trial showing no significant effect on pain or analgesic use.³⁹ Nevertheless, there is some evidence suggesting its use in severely painful CP.⁴⁰ Studies on treatment of painful CP with antioxidants have also shown mixed results. A British RCT of CP patients treated with antioxidants did not show benefit in terms of pain, hospital admissions, or opiate use⁴¹; however, several other RCTs investigating antioxidant therapy for painful CP did show significant reduction in pain,^{42,43} as did a 2015 meta-analysis.⁴⁴ Cannabis and cannabinoids have also been studied as a potential treatment for CP patients^{45,46}; however, evidence is limited and high-quality studies are needed.

Exocrine Pancreatic Insufficiency and Nutrition

Malabsorption caused by reduced production and/or secretion of pancreatic digestive enzymes often develops in

CP patients. This process can manifest with diarrhea, steatorrhea, weight loss, bloating, flatulence, and nutritional deficiencies, including fat-soluble vitamin deficiencies. In patients presenting with these symptoms, alternative diagnoses such as malignancy should be ruled out. EPI can be diagnosed by measuring fecal elastase, an indirect measure of pancreatic function. A fecal elastase level of less than 50 µg/g is suggestive of severe EPI, less than 100 µg/g of definite EPI, and 100 µg/g to 200 µg/g is considered indeterminate. Fecal elastase may be abnormally low in patients with watery diarrhea and may not detect cases of mild EPI.⁴⁷ Direct pancreatic function tests involve endoscopic or tube-based stimulation of the pancreas with secretin or cholecystokinin with subsequent measurement of pancreatic secretions and are more sensitive for mild EPI. These tests are limited by availability, cost, and invasiveness. Other indirect tests (eg, the ¹³C-mixed triglyceride breath test and 72-hour fecal fat measurement) are cumbersome to perform.³ Therefore, fecal elastase remains the first-line diagnostic test for EPI.⁴⁷

Treatment of EPI is focused on oral replacement of endogenously produced pancreatic enzymes and can be initiated empirically in symptomatic patients with indeterminate fecal elastase levels.⁴⁷ Several different PERTs containing a mixture of lipases, proteases, and amylases are commercially available and have been shown to significantly reduce stool frequency^{48,49} and fecal fat excretion^{48,49} and improve stool consistency,^{48,49} body mass index,⁵⁰ and symptoms^{49,50} in clinical trials of patients with EPI. A reasonable starting dose of PERT should contain at least 40,000 USP/day of lipase and can be up-titrated as needed to achieve satisfactory control of symptoms. PERT should be administered during meals.³ It is important to note that treatment with PERT does not affect fecal elastase levels, and therefore fecal elastase should not be used to gauge treatment response. Instead, treatment response can be assessed by improvement in symptoms, weight gain, and improvement in nutritional deficiencies. In addition to pharmacotherapy, dietary modifications, including consumption of smaller more frequent meals and adopting a diet with lower fat content, may improve symptoms.⁴⁷

CP patients are at risk for deficiencies of minerals⁵¹ and of fat-soluble vitamins A, D, E, and K.⁵² Studies have shown improvement in these deficiencies with vitamin supplementation,⁵³ and treatment with proton pump inhibitors or histamine 2 receptor antagonists has been shown to improve fat absorption with PERT.⁵⁴

Patients with CP are at increased risk for osteoporosis⁵⁵ and should be screened with a bone density scan every 2 years.⁴⁷ Vitamin D and calcium deficiencies should be identified and treated.⁵⁶ Endocrinology consultation and initiation of pharmacotherapy with bisphosphonates or

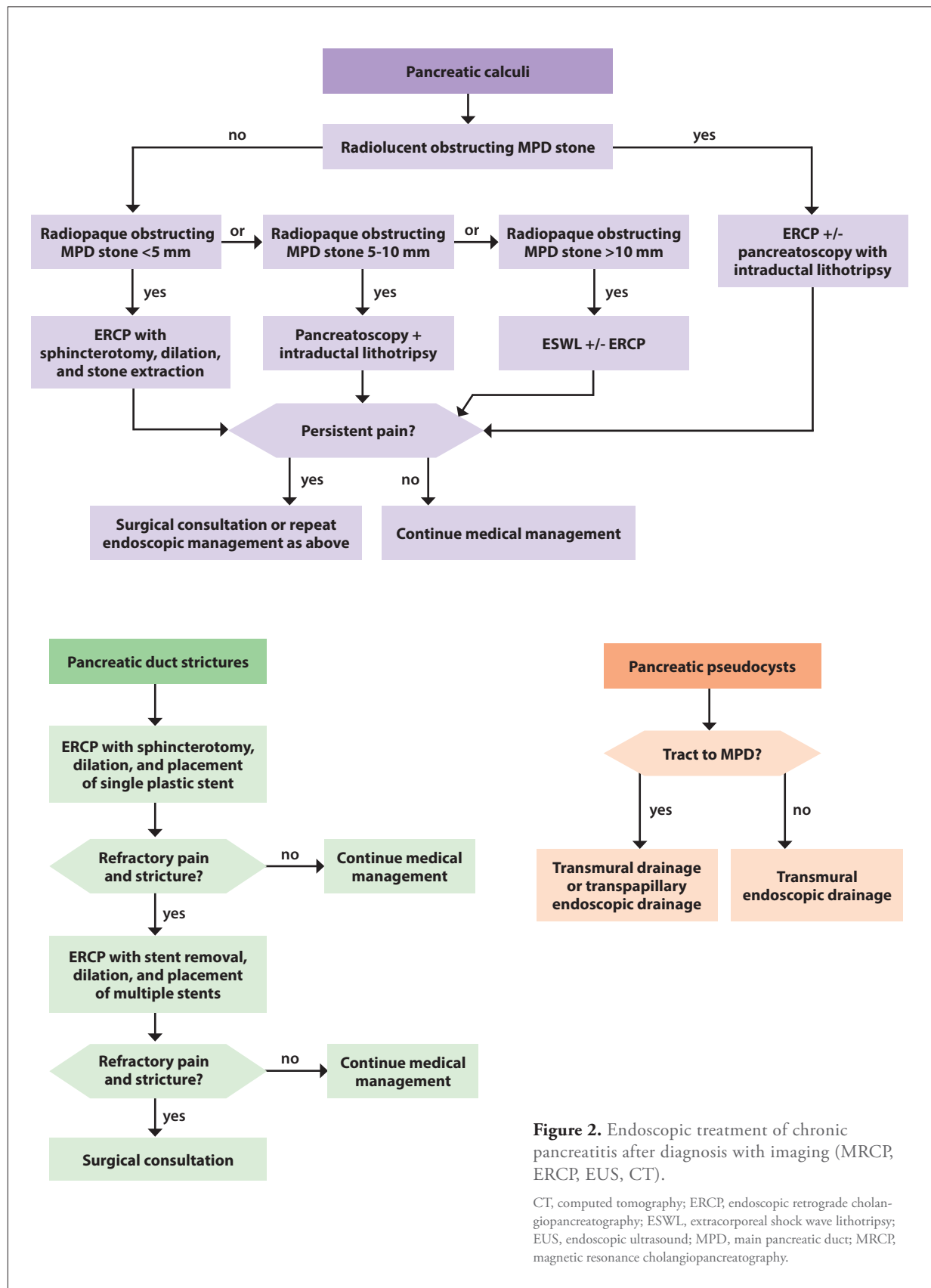


Figure 2. Endoscopic treatment of chronic pancreatitis after diagnosis with imaging (MRCP, ERCP, EUS, CT).

CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; ESWL, extracorporeal shock wave lithotripsy; EUS, endoscopic ultrasound; MPD, main pancreatic duct; MRCP, magnetic resonance cholangiopancreatography.

denosumab should be strongly considered in CP patients with osteoporosis.

Endocrine Insufficiency

The pancreas plays an important metabolic role through insulin, glucagon, somatostatin, and pancreatic polypeptide production. CP patients can develop complex endocrine dysfunction because of the destruction of alpha and beta cells.⁵⁷ Additionally, EPI in CP patients leads to diminished secretion of the incretin glucose-dependent insulinotropic polypeptide (GIP), further affecting insulin release. Treatment of EPI improves secretion of GIP.⁵⁸ Diabetes caused by CP is known as pancreatogenic or type 3c diabetes mellitus. The diagnostic criteria include objective evidence of EPI, abnormal pancreatic imaging, and lack of serum biomarkers for type 1 diabetes mellitus.⁵⁹ Evidence regarding optimal treatment of endocrine insufficiency in CP patients is limited. Many patients are treated with insulin; however, caution should be exercised as patients with endocrine insufficiency have impaired glucagon production and are at high risk for hypoglycemia.⁶⁰ Glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase 4 inhibitors typically have been avoided because of an early study showing an increased risk for AP and pancreatic cancer.⁶¹ However, a recent meta-analysis of clinical trial data did not show an increased risk of pancreatic cancer with GLP-1 therapy.⁶² Furthermore, several meta-analyses have shown no increased risk of pancreatitis in patients taking GLP-1 agonists, and recent observational studies showed a reduced lifetime risk of pancreatitis⁶³ and a reduced risk of complicated pancreatitis in diabetic patients on GLP-1 agonists.⁶⁴ Further high-quality studies are needed to explore the relationship between GLP-1 medications and pancreatitis.

Pancreatic Cancer

CP is a well-established risk factor for pancreatic cancer, with pooled data from a meta-analysis revealing a relative risk of 13.3 in all CP patients rising to 69.0 in hereditary pancreatitis.⁶⁵ Currently, American Gastroenterological Association (AGA) guidelines advise consideration of pancreatic cancer screening in patients at high risk, including those with strong family history, genetic syndromes with increased risk of pancreatic cancer, and patients with hereditary pancreatitis. Screening modalities include magnetic resonance imaging and EUS. The guidelines recommend starting screening at age 35 years in patients with Peutz-Jeghers syndrome, 40 years in patients with hereditary pancreatitis, 50 years in other high-risk individuals, or when the patient is 10 years younger than disease onset in a family member.⁶⁶ Given the increased risk of pancreatic cancer in all CP patients, further studies are needed to evaluate whether all CP patients may benefit

from screening. The US Preventive Services Task Force does not recommend screening for pancreatic cancer, including in patients with CP.⁶⁷

Interventional Management of Chronic Pancreatitis

Proposed endoscopic treatment algorithms for CP are presented in Figure 2.

Pancreatic Calcifications

Pancreatic stones can cause obstruction of the main pancreatic duct (MPD), leading to elevated intraductal pressure, inflammation, and pain. Both endoscopic and surgical treatment of pancreatic calcifications focus on stone clearance and relief of the obstruction in the main duct.⁶⁸ Endoscopic treatment approaches include extracorporeal shock-wave lithotripsy (ESWL) with or without endoscopic retrograde cholangiopancreatography (ERCP), pancreatoscopy with intraductal lithotripsy, and ERCP with standard stone removal methods, including sphincterotomy, dilation, and balloon or basket extraction.

A Belgian RCT of CP patients with greater than 4-mm obstructing stones of the MPD found no significant difference in procedural complications or recurrence of pain in patients treated with ESWL alone as compared with ESWL followed by ERCP with stone retrieval and pancreatic stent placement (38% vs 45% of patients) at approximately 2 years of follow-up.⁶⁹ An observational study also showed similar efficacy with respect to pain relief and rates of adverse events when comparing ESWL alone with ESWL and ERCP.⁷⁰

No RCTs have investigated pancreatoscopy and intraductal lithotripsy for treatment of CP. An American retrospective study compared CP patients with large (>5 mm) MPD stones who underwent ESWL followed by ERCP (n=240) with those who underwent pancreatoscopy and intraductal lithotripsy (n=18). Pancreatoscopy with intraductal lithotripsy was found to be more efficient (requiring fewer procedures to clear stones), and the procedures were significantly shorter. The exception was for patients with stones larger than 10 mm, in which ESWL followed by ERCP was more efficient. No significant difference in rate of adverse events or pain relief was appreciated between both groups.⁷¹ A Dutch retrospective study of 37 CP patients compared pancreatoscopy/electrohydraulic lithotripsy (EHL) with ESWL followed by endoscopic retrograde pancreatography (ERP). The study included patients with 1 or more obstructive PD stones (>5 mm) in the head or neck region of the pancreas and found stone recurrence in 36.8% of patients in the EHL group as compared with 61.1% of patients in the pancreatoscopy/EHL group. Opioid use fell from 53% of patients at baseline

to 16% at 6-month follow-up, and rebounded to 32% at long-term follow-up.⁷² A meta-analysis comparing pancreatoscopy/intraductal lithotripsy vs ESWL for treatment of CP with symptomatic PD stones found no significant difference in stone clearance, symptom improvement, or rate of adverse events between the 2 interventions.⁷³

A large Japanese retrospective study of treatment of pancreatolithiasis included 479 patients treated with ESWL, 83 treated with endoscopy alone, and 135 treated with surgery. A significantly higher proportion of the endoscopy group had stones smaller than 10 mm (86.7%) compared with the ESWL group (46.6%). Rates of stone clearance (87.9% vs 49.2%) were significantly higher in the endoscopy group and rate of recurrence of abdominal pain was significantly lower in the endoscopy group (8.4% vs 17.6%) compared with the ESWL group.⁷⁴ ERCP alone is recommended by AGA and American Society for Gastrointestinal Endoscopy (ASGE) guidelines for endoscopic treatment of MPD stones smaller than 5 mm.^{75,76}

In summary, for radiopaque obstructing MPD stones smaller than 5 mm, ERCP with typical stone removal techniques, including sphincterotomy, dilation, and balloon or basket stone extraction is reasonable. For radiopaque obstructing MPD stones of 5 to 10 mm pancreatoscopy with intraductal lithotripsy is likely the most efficient approach. For radiopaque obstructing stones larger than 10 mm, ESWL with or without ERCP is the optimal nonoperative therapy. Nevertheless, it is important to note that the availability of ESWL is limited in the United States, and ESWL is generally only performed at high-volume pancreatic disease centers. For treatment of radiolucent stones, minimal evidence exists to guide practice but ERCP with or without pancreatoscopy and intraductal lithotripsy is recommended by the ASGE guidelines.⁷⁶ Nevertheless, pancreatoscopy offers the theoretical benefit of direct visualization and targeting with intraductal lithotripsy of stones which cannot be seen on fluoroscopy.

Strictures and Abnormalities of the Biliary Tree

Stricture of the MPD is a common complication of CP and is suspected to contribute to pain and inflammation by raising intraductal pressure. Therapy is focused on relief of the obstruction.⁶⁸ There is strong evidence for endoscopic intervention to treat PD strictures in CP patients. A German prospective study of 19 patients with PD strictures treated with ERP, sphincterotomy, PD dilation, and stent placement found complete pain relief in 57% of patients at 5 years of follow-up.⁷⁷ A second German study of 93 patients with painful CP and dominant PD stricture treated by stent drainage found complete or partial pain relief in 74% of patients at 6-month follow-up and sustained pain relief in 65% at approximately 5 years of follow-up; adverse events included pancreatitis in 4% of patients and

abscess formation in 2%.⁷⁸ A third study of 23 patients with painful CP and MPD strictures treated with balloon dilation and 6 months of MPD stenting found 74% of patients were analgesic-free at stent removal and 52% at 1 year following stent removal.⁷⁹ A fourth study investigating stenting of dominant PD strictures with mean follow-up of 3 years found significant reductions in narcotic use and hospital visits and significant increases in weight after 6 months of stenting; 36% of patients required endoscopic reintervention during the follow-up period.⁸⁰

In CP patients with dominant PD strictures who have refractory symptoms to placement of a single stent, placement of multiple stents may increase the likelihood of successful treatment. An Italian cohort study of 19 patients with severe CP with a dominant PD stricture in the pancreatic head that had failed to respond to decompression with a single stent found that 84% were asymptomatic at mean follow-up of 38 months following single stent removal and placement of multiple stents.⁸¹ A Belgian retrospective study of CP patients with MPD strictures found that patients initially treated with 2 stents were less likely to have a successful treatment outcome and had higher levels of pain compared with patients treated with a single stent at median follow-up of 84 months.⁸²

Interestingly, MPD width following stenting does not correlate with symptom relief. A study of endoscopic stenting in advanced CP found that pain was improved by stenting in 71% of patients whose duct caliber increased or remained the same postprocedurally and in 50% of patients whose duct caliber decreased.⁸³

Different types of stents and stent diameters have been studied for CP treatment. An American study found that PD stenting with larger diameter plastic stents (10F) had a significantly lower rate of hospitalization for abdominal pain than patients treated with 8.5F stents.⁸⁴ Studies have shown fully covered self-expanding metal stents (FCSEMS) to be efficacious but associated with a higher likelihood of adverse events. A Korean study of 35 patients treated with FCSEMS for refractory pancreatic strictures found 82.9% to have cessation or more than 50% reduction of analgesic use for at least 3 months postprocedure. However, stent-related strictures occurred in 48.9% of patients.⁸⁵ In a recent multicenter international clinical trial investigating FCSEMS to treat painful CP-induced PD strictures, only 26.1% of patients experienced complete or partial pain relief at 6 months of follow-up. Additionally, 31.3% of patients experienced serious adverse events, and 47.7% experienced stent migrations.⁸⁶ A meta-analysis comparing plastic stents to FCSEMS in treatment of refractory PD strictures found insignificant differences in pain relief but increased risk of adverse events with FCSEMS.⁸⁷

The optimal strategy for stent replacement has not been established, but strategies include scheduled

replacement every 3 months and replacement based on symptom recurrence.⁶⁸ In summary, all patients with a dilated MPD thought to be due to obstruction should have a stent placed in an attempt for ductal decompression and possible improvement in pain. Initial endoscopic management for PD stricture should consist of placement of a single plastic stent of the highest possible diameter. Patients who do not respond to a single stent can undergo stent removal with dilation and placement of multiple stents. Plastic stents are preferable to FCSEMS given their lower risk for adverse events and stent migration.

Pancreatic Pseudocysts

Pancreatic pseudocysts are fluid collections in the pancreas surrounded by an inflammatory capsule. Pseudocysts can remain asymptomatic, but intervention is indicated when pseudocysts become symptomatic, obstructive, ruptured, hemorrhagic, or infected. Drainage can be accomplished percutaneously, endoscopically, and surgically. Endoscopic approaches include transmural drainage via the stomach (endoscopic cystogastrostomy) or duodenum (endoscopic cystoduodenostomy) and transpapillary drainage through the PD, which can be performed if there is a tract connecting the pseudocyst to the PD.⁸⁸ A RCT of 40 patients with pancreatic pseudocysts measuring at least 6 cm that compared endoscopic and surgical cystogastrostomy found no significant difference in pseudocyst recurrence or adverse events after 2-year follow-up but significantly lower hospital length of stay and cost with endoscopic management.⁸⁹ A trial of endoscopic transpapillary cyst drainage in patients with pancreatic pseudocysts (the majority of whom also had CP) found that 86.7% of patients had resolution of pancreatic pseudocysts at an average of 15 months of follow-up.⁹⁰ A prospective study assessing the use of self-expanding metal stents to drain pancreatic fluid collections in 33 patients (28 with CP) found resolution of pseudocysts in 93% of patients, with complications occurring in 15% of patients.⁹¹

In summary, pancreatic pseudocyst drainage can be accomplished with several techniques, but the first-line therapy should be endoscopic drainage with plastic stents. In patients who are not candidates for endoscopy or surgery, medical therapy with octreotide can be attempted.

Management of Nonresponsive Chronic Pancreatitis

Celiac Plexus Nerve Block

Celiac plexus nerve block is an invasive procedure characterized by targeted injection of the celiac plexus with local anesthetic in order to blunt transmission of pain signals from afferent nociceptors to the central nervous system.⁶⁸ Several observational studies have demonstrated pain

improvement in CP patients treated with celiac plexus nerve block. A prospective study of EUS-guided celiac plexus nerve block found that significant improvement in pain scores was achieved in 55% of patients, with 26% of patients deriving sustained benefit beyond 3 months postprocedurally.⁹² A meta-analysis assessing EUS-guided celiac plexus nerve block in CP patients found that the procedure improved pain in approximately 51% of patients.⁹³ A randomized trial comparing EUS-guided celiac plexus nerve block with computed tomography-guided celiac plexus nerve block in CP patients showed more persistent pain relief in the EUS-guided group.⁹⁴ A retrospective study of patients undergoing multiple EUS-guided celiac plexus nerve block procedures found that pain relief following initial celiac plexus nerve block was a predictor of response to subsequent blocks and that no major adverse events occurred with multiple blocks.⁹⁵ The EPOCH randomized sham-control trial is currently being performed to further assess the efficacy of EUS-guided celiac plexus nerve block for the treatment of pain secondary to CP.⁹⁶

In summary, celiac plexus nerve block is effective for temporary relief of pain in some CP patients. An EUS-guided approach is preferable to a CT-guided approach, and repeating a celiac plexus nerve block is safe and more likely to be effective in patients who previously responded to the procedure.

Surgery

Surgical treatment of CP is typically considered in patients who have not responded to medical and endoscopic therapy. Surgical interventions include total pancreatectomy, pancreatic head resection and/or drainage, pancreaticoduodenectomy, and distal pancreatectomy. An in-depth description of surgical management is beyond the scope of this article. However, a study of 493 patients who underwent different surgical interventions for CP found that 5-year survival was 81.3% and 10-year survival was 63.5%, 73.1% of patients were off opioids, and 41.3% of patients were insulin dependent at >5 years of follow-up.⁹⁷

Endoscopy vs Surgery

A number of studies have compared endoscopic management with surgery for treatment of painful CP. The ESCAPE clinical trial consisted of 88 patients with painful CP randomized to treatment with early surgery or endoscopy. At follow-up (mean 98 months), in the early surgery group, Izbicki pain scores were significantly lower (33 vs 51), complete pain relief was observed in a higher percentage of patients (45% vs 20%), and patients required a significantly lower number of repeat endoscopic or surgical interventions (1 vs 4). No significant differences were observed with respect to treatment complications. However, in a subgroup analysis, patients

who underwent endoscopic intervention with duct clearance did not have a significant difference in Izbicki pain scores, complete pain relief, or quality of life.⁹⁸ A second RCT of 39 CP patients randomized to endoscopic or surgical PD decompression found that after 5 years of follow-up, patients randomized to endoscopy had undergone a greater number of procedures (12 vs 4) and had a lower likelihood of complete pain relief (38% vs 80%), although no significant difference in mean Izbicki pain score was appreciated between the 2 groups.⁹⁹

Although studies have shown surgical management to be superior to endoscopic therapy with respect to pain relief and the number of procedures required, patients who underwent endoscopy with complete PD clearance attained similar pain relief to patients who underwent surgical treatment.⁹⁸ Therefore, in patients with a high probability of ductal clearance, such as those without obstruction in the tail of the pancreas, an endoscopy-first approach is reasonable, especially considering that many surgeons only operate once endoscopy has failed and that many patients prefer a less invasive initial approach.³ Gastroenterologists should discuss the risks and benefits of each approach with patients and offer them surgical consultation. Endoscopic treatment approaches for painful CP are heterogeneous, and further studies are needed to compare outcomes of specific endoscopic therapies with specific surgical interventions and to better identify ideal candidates for each approach.

Total Pancreatectomy With Islet Autotransplantation

Total pancreatectomy with islet autotransplantation (TPIAT) consists of complete surgical pancreatic resection followed by autologous transplantation of pancreatic islet cells into the portal vein. It is an emerging treatment for painful CP refractory to medical, endoscopic, and alternative surgical management. Observational and case series data have shown promising results. A study of 16 patients who underwent TPIAT found insulin independence in 53% and significant pain reduction in 93% of patients postoperatively.¹⁰⁰ A study of 742 patients who underwent TPIAT found pain relief in 82% of patients at 10 years and 90% at 15 years, 20% of patients were insulin independent 10 years postoperatively, and the 10-year survival rate was 72%.¹⁰¹ A study of 195 patients who underwent TPIAT found insulin independence in 23% of patients at 5 years postoperatively, median oral morphine equivalents decreased from 214 mg/kg preoperatively to 69 mg/kg 5 years postoperatively, quality of life was significantly improved, and 5-year survival was 92.3%.¹⁰² A retrospective study of patients with minimal change in CP who underwent TPIAT found that 58.3% of patients were opioid free and 36.9% were insulin independent postoperatively.¹⁰³ A recently published large multicenter

study (POST) of 384 patients undergoing TPIAT for CP or recurrent AP found that at 1-year follow-up, opioid use decreased from 61% of patients to 24% of patients, daily abdominal pain decreased from 65% of patients to 23%, 20% of patients were insulin independent, and there was significant improvement in quality-of-life scores. Response to TPIAT was independent of CP etiology, length of disease, and prior pancreatic surgery. One-year survival was 98.3%.¹⁰⁴ The POST cohort of patients had a variety of risk factors for CP. Pain, nutritional deficiencies, and disease burden were high in the study cohort, and many patients had undergone prior endoscopic or surgical interventions. The POST results suggest that TPIAT is a promising option for treatment of painful CP in patients with a high burden of disease regardless of etiology. Poor candidates for TPIAT include patients with ongoing substance use disorder, patients with pancreatic cancer, and patients who are poor surgical candidates owing to severe cardiopulmonary disease, liver disease, or deconditioning.¹⁰⁵ Additionally, TPIAT remains limited by availability and is only offered at high-volume pancreatic disease centers in the United States. Nevertheless, TPIAT represents a promising treatment option for patients with painful CP in which other therapies have been exhausted.

Conclusion

CP is a debilitating disease that is challenging to treat. Medical management is focused on identifying and addressing disease risk modifiers and managing the various complications of CP, including pain, endocrine insufficiency, and EPI. Both endoscopic and surgical interventions to treat CP seek to alleviate pain via decompression of the MPD, which can become obstructed as a result of pancreatic calcifications and/or strictures. TPIAT represents a promising emerging therapy for painful CP refractory to medical management and will likely be offered to an expanding group of patients in the years ahead.

Disclosures

The authors have no relevant conflicts of interest to disclose.

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