JAMA Surgery | Review

Etiology, Diagnosis, and Modern Management of Chronic Pancreatitis
A Systematic Review

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IMPORTANCE The incidence of chronic pancreatitis is 5 to 12 per 100 000 adults in industrialized countries, and the incidence is increasing. Treatment is multimodal, and involves nutrition optimization, pain management, and when indicated, endoscopic and surgical intervention.

OBJECTIVES To summarize the most current published evidence on etiology, diagnosis, and management of chronic pancreatitis and its associated complications.

EVIDENCE REVIEW A literature search of Web of Science, Embase, Cochrane Library, and PubMed was conducted for publications between January 1, 1997, and July 30, 2022. Excluded from review were the following: case reports, editorials, study protocols, nonsystematic reviews, nonsurgical technical publications, studies pertaining to pharmacokinetics, drug efficacy, pilot studies, historical papers, correspondence, errata, animal and in vitro studies, and publications focused on pancreatic diseases other than chronic pancreatitis. Ultimately, the highest-level evidence publications were chosen for inclusion after analysis by 2 independent reviewers.

FINDINGS A total of 75 publications were chosen for review. First-line imaging modalities for diagnosis of chronic pancreatitis included computed tomography and magnetic resonance imaging. More invasive techniques such as endoscopic ultrasonography allowed for tissue analysis, and endoscopic retrograde cholangiopancreatography provided access for dilation, sphincterotomy, and stenting. Nonsurgical options for pain control included behavior modification (smoking cessation, alcohol abstinence), celiac plexus block, splanchnicectomy, nonopioid pain medication, and opioids. Supplemental enzymes should be given to patients with exocrine insufficiency to avoid malnutrition. Surgery was superior to endoscopic interventions for long-term pain control, and early surgery (<3 years from symptom onset) had more superior outcomes than late surgery. Duodenal preserving strategies were preferred unless there was suspicion of cancer.

CONCLUSIONS AND RELEVANCE Results of this systematic review suggest that patients with chronic pancreatitis had high rates of disability. Strategies to improve pain control through behavioral modification, endoscopic measures, and surgery must also accompany management of the sequalae of complications that arise from endocrine and exocrine insufficiency.

JAMA Surg. 2023;158(6):652-661. doi:10.1001/jamasurg.2023.0367
Published online April 19, 2023.

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Chronic pancreatitis (CP) is caused by progressive inflammation leading to the distortion and destruction of acinar structure and function. The most common factor that incites such pancreatic inflammation is alcohol, although smoking, anatomic variations leading to chronic duct obstruction, genetic predisposition, autoimmune diseases, and recurrent episodes of acute pancreatitis are also risk factors. Treatment is multimodal, requiring nutritional optimization, medical therapies, pain control, endoscopic and/or surgical interventions, and management of complications associated with loss of pancreatic endocrine and exocrine function, such diabetes and malnutrition. Patients with CP are also at increased risk of malignancy, although there are no routine screening guidelines for pancreatic adenocarcinoma (PDAC). The purpose of this review was to systematically summarize the most recent, highest-evidence literature in order to provide an overview of the most common causes, diagnosis, treatment, and prognosis of patients with CP with a focus on surgical interventions.

Methods

A systematic literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines (**Figure 1**). PubMed, Cochrane Library,

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Embase, and Web of Science were queried using the key words "chronic pancreatitis," "chronic pancreatitis surgery," and "chronic pancreatitis treatment." Initial filters were human participants, publication date (excluding publications published >25 years ago), and age older than 18 years. Titles and abstracts were screened by 2 independent reviewers (S.M.C. and T.S.K.), and irrelevant articles were excluded. The remaining articles underwent full-text review to exclude case reports, pediatric studies, publications in languages other than English, publications focused on diseases other than CP, animal studies, in vitro studies, nonsystematic reviews, studies that did not clearly describe their methodology, pilot studies, cohort studies with CP groups containing fewer than 10 patients, nonsurgical technical articles (ie, plastic vs metal stent, number of stents, single- or double-layer sutures), articles focusing on endoscopic interventions alone, and articles without an available full text for evaluation. Quality of evidence was determined independently by T.S.K. and S.M.C. and rated based on the Oxford Center for Evidence Based Medicine standards (**Table 1**).[1-75]

In order to limit this review to 75 publications as required, if multiple articles existed on a given topic, higher level–evidence publications, journal impact factor, date of publication, experience of lead authorship in the management of CP, and total number of citations were taken into consideration. Discrepancies were discussed by 2 authors (T.S.K and S.M.C.) to review main article findings, methodology, and level of evidence until consensus was met. During the initial screening stage, there was disagreement in less than 10% of the initial articles screened, which ultimately underwent full-text review. After full-text review, 246 articles were discussed by the 2 reviewers, as all articles had met inclusion and exclusion criteria, although there was redundancy in subject matter. These 246 articles were analyzed to determine which studies were of the highest impact and influence on clinical practice based on the previously mentioned metrics.

Key Points

Question What are the most common etiologies, symptoms, treatments, and outcomes for patients with chronic pancreatitis?

Findings In this systematic review of 75 articles, risk factors for chronic pancreatitis include alcohol abuse, gallstones, and genetic susceptibility, and the most common symptom is abdominal pain. Treatment requires nutritional optimization, pain management, and endoscopic interventions/surgery when conservative measures have failed, and surgery is more effective than endoscopy in long-term pain relief and quality-of-life metrics.

Meaning Management of chronic pancreatitis is multimodal and multidisciplinary; when indicated, surgical intervention may result in long-term pain relief and improved quality of life.

Results

A total of 3110 articles were initially identified, and 75 studies remained after removing duplicates, irrelevant articles, and those that met our exclusion criteria (Figure 1). Characteristics of included articles are described in Table 1.[1-75]

Pathophysiology and Risk Factors

CP is incited by recurrent cellular damage resulting in inflammation and ultimately, distortion, calcification, and fibrosis. Cellular injury is most frequently caused by alcohol, smoking, gallstones, genetic variants, and idiopathic etiologies. Ten percent of patients develop CP after their first known episode of acute pancreatitis; 30% of patients with recurrent episodes of acute pancreatitis progress to CP.[1]

The risk factors for CP can be summarized by 2 severity classification systems: (1) toxic-metabolic, idiopathic, genetic, autoimmune, recurrent, and severe autoimmune–associated CP and obstruction (TIGAR-O) and (2) multiple risk factors including alcohol consumption, nicotine, nutritional factors (hyperlipidemia), hereditary, efferent duct disorders (pancreas divisum, annular pancreas), immunologic, and miscellaneous and rare metabolic disorders (MANNHEIM).[2] Patients consuming 25 g to 50 g of alcohol daily are 1.5 times more likely to develop CP, and the risk increase is dose dependent.[3] Smoking 15 to 25 cigarettes per day increases CP risk by 2 fold.[4]

Genetic variants account for less than 10% of CP. *SPINK1* encodes a trypsin inhibitor. A loss-of-function variant results in autodigestion from inability to inhibit prematurely activated trypsinogen.[5] A gain-of-function variant in *PRSS1* leads to an increase in active intrapancreatic trypsin and thus, autodigestion.[5] *CFTR* thins proteinaceous acinar cell secretions through bicarbonate regulation, consequently, variants in this gene lead to formation of protein plugs.[6] *CTRC* (chymotrypsin) and *CASR* (regulates calcium in pancreatic secretions) are also implicated in CP but are less common.[4]

Clinical Presentation

A total of 75% of patients with CP present with abdominal pain,[7] but the severity and duration of abdominal pain symptoms do not correlate with the degree of anatomic pancreatic destruction.[8] Although less common, approximately 10% of patients never experience abdominal pain and may present with symptoms of malabsorption. Weight loss is the second most common initial symptom in 22% and is multifactorial—due to loss of exocrine function, insulin deficiency, and/or food aversion secondary to pain. Twenty-eight percent of patients present with diabetes, 11% with jaundice, and 3% with steatorrhea.[7]

Assessment and Diagnosis

CP diagnosis requires synthesis of patients' history, examination, laboratory studies, and imaging. Symptoms of abdominal pain, malnutrition, and steatorrhea, new-onset diabetes, and risk factors such as history of acute pancreatitis, smoking, alcohol use, family history of CP, PDAC, and/or other genetic factors should be ascertained. It is critical to assess the impact of symptoms on patient function and quality of life (QoL)—including frequency and duration of hospital admissions, ability to work, and ability to complete activities of daily living.

Unlike in acute pancreatitis, there are no standard laboratory tests to aid in the diagnosis of CP. Lipase is often within normal limits. For specific patients with risk factors for PDAC or imaging findings suspicious of malignancy, carbohydrate antigen 19-9 should be checked. However, cholecystokinin stimulation, secretin stimulation, fecal elastase, carbon 13 (^{13}C) mixed triglycerides, and serum trypsin/chymotrypsin all may measure pancreatic exocrine insufficiency, but insufficiency requires destruction of 90% pancreatic acinar cells, and steatorrhea can also be diagnosed clinically. Autoimmune pancreatitis may lead to CP, but universal antibody screening

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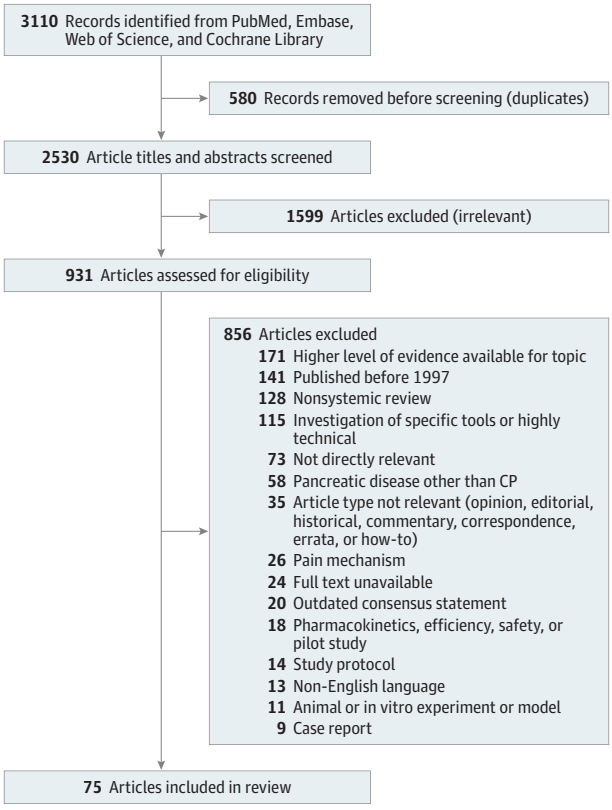
Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Flow Diagram



CP indicates chronic pancreatitis.

is not recommended unless a patient has a family history or other features concerning for autoimmune pancreatitis.[9] Genetic testing is reserved for patients with a strong family history of CP, pulmonary symptoms raising suspicion for cystic fibrosis, and young age at onset. Findings may help guide multidisciplinary care planning, particularly if details regarding expected risk of PDAC can thus be established.

Computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), and endoscopic retrograde cholangiopancreatography (ERCP) are useful to aid in the diagnosis CP (**Table 2**).[9] CT is noninvasive and can exclude other causes of chronic abdominal pain. MRCP has better resolution than CT but is more expensive and requires more time. However, administering secretin during MRCP enhances visualization of ductal architecture—although it may exacerbate symptoms in patients with recent or ongoing pancreatitis flares.

ERCP is both the most sensitive and specific test to diagnose CP (82% sensitivity and 96% specificity)[10] and is both diagnostic and therapeutic; however, it evaluates ductal architecture only and does not visualize the parenchyma. Of all imaging modalities, ERCP is the most invasive and confers risks of intestinal perforation and post-ERCP pancreatitis.

CT, magnetic resonance imaging (MRI), and ERCP detect advanced structural changes associated with chronic inflammation, but EUS, in addition to providing a window to perform tissue biopsies when there is concern for cancer, may be useful to detect earlier structural changes associated with CP. However, the structural changes detected by EUS may not be specific for CP because obesity, smoking, and chronic alcohol consumption may also cause similar structural changes. The Rosemont Criteria was established to diagnose CP based on major and minor parenchymal and ductal findings on EUS, but a diagnosis of CP remains a clinical diagnosis.

Although ERCP has the highest specificity and sensitivity in the diagnosis of CP, it would not be able to be used in isolation as some patients have minor ductal changes with parenchymal disease. Thus, the imaging modalities chosen in the workup for CP should lead to a sufficient understanding of parenchymal anatomy, ductal anatomy, and if a biopsy is required, then EUS needs to be performed.

Imaging may distinguish CP from PDAC.[11] Groove pancreatitis, a focal pancreatitis that preferentially affects the region between the pancreatic head, duodenum, and common bile duct, may be mistaken for PDAC. If calcifications appear to disperse over time, it is possible that an enlarging cancer may be displacing them. The "double-duct sign," dilation of both the common bile duct and the pancreatic duct, raises concern for an obstructing cancer. The "duct-penetrating sign," on the other hand, is a gradual tapering or narrowing of the pancreatic duct as it crosses a compressible, inflammatory focus.[11]

Treatment

Pain is the leading cause of hospitalization, disability, and unemployment in patients with CP. The most commonly used pain scale to measure the effectiveness of a given intervention to improve CP-related pain in clinical trials is the Izbicki pain score. The Izbicki pain score incorporates frequency of pain, intensity of pain, analgesic use, and ability or inability to work to generate a score from a total of 100. Other scales such as the comprehensive pain assessment tool (COMPAT) questionnaire have been validated to characterize clinical pain symptoms.[12] Phillips and colleagues[13] recently proposed using a physiologic approach to pain characterization through quantitative sensory testing. Quantitative sensory testing involves stimulating specific dermatomes and measuring the effect on central and peripheral pain pathways.[13] This technology may provide an additional data point when determining the most efficacious, patient-centered treatment algorithm.

First-line approaches to pain treatment include alcohol and smoking cessation and use of nonopioid medications such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). Smoking alone is associated with a 2-fold increase in risk of pain.[14] In addition to NSAIDS and acetaminophen, pregabalin has been shown to reduce pain by 36% after 3 weeks—even in patients who already underwent endoscopic interventions and in patients taking strong opioids.[15] Tricyclics may be another nonopoid option in the management of CP; however, to our knowledge, there are no large randomized trials that have determined efficacy.

Celiac plexus block and celiac plexus neurolysis are nonsurgical, nonnarcotic modes of pain control, but current evidence shows that although they reduce pain in 50% of patients in the short term, the effect is temporary, lasting for a few weeks to months.[16] Thoracoscopic splanchnicectomy is effective for 6 months, but pain reduction becomes insignificant by 24 months postoperatively.[17] Still, patients already taking large doses of narcotics are less likely to have improved pain symptoms after thoracoscopic splanchnicectomy.[18]

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Table 1. Included Articles and Level of Evidence According to Abbreviated Oxford Classification

Source	Study design	Level of evidence (Oxford)
General overview		
Singh et al,[4] 2019	Systematic review	1
Madan et al,[73] 2013	Prospective cohort study	2
Epidemiology, etiology, and risk factors		
Sankaran et al,[1] 2015	Systematic review and meta-analysis	1
Schneider et al,[2] 2007	Systematic review	1
Samokhvalov et al,[3] 2015	Systematic review and meta-analysis	1
Tang et al,[5] 2020	Systematic review and meta-analysis	1
Zhao et al,[6] 2017	Systematic review and meta-analysis	1
Thompson et al, 2021[7]	Systematic review	1
Levy et al, 2014[57]	Systematic review and meta-analysis	1
Baltatzis et al,[74] 2019	Systematic review	1
Diagnosis		
Wilcox et al,[8] 2015	Prospective cohort study	3
Zeng et al,[9] 2019	Cross-sectional study	4
Issa et al,[10] 2017	Systematic review and meta-analysis	1
Schima et al,[11] 2020	Expert opinion	5
Endoscopy vs surgery		
Issa et al,[31] 2020	Randomized controlled trial	1
Cahen et al,[32] 2011	Randomized controlled trial	1
Surgical approaches		
Ahmed et al,[33] 2012	Retrospective cohort study	3
Ke et al,[35] 2018	Retrospective cohort study	3
Yang et al,[36] 2014	Systematic review	1
Yang et al,[37] 2014	Systematic review	1
Sakorafas et al,[38] 2000	Retrospective cohort study	3
Izbicki et al,[39] 1998	Randomized controlled trial	1
Bachmann et al,[40] 2013	Randomized controlled trial	1
Witzigmann et al,[41] 2003	Prospective cohort study	3
Diener et al,[42] 2017	Randomized controlled trial	1
Diener et al,[43] 2008	Systematic review and meta-analysis	1
Merdrignac et al,[44] 2016	Retrospective cohort study	3
Müller et al,[45] 2008	Randomized controlled trial	1
Ratnayake et al,[46] 2020	Systematic review and meta-analysis	1
Gurusamy et al,[47] 2016	Systematic review and meta-analysis	1
Klaiber et al,[48] 2016	Randomized controlled trial	1
Zhou et al,[49] 2015	Systematic review and meta-analysis	1
Zhao et al,[50] 2017	Systematic review and meta-analysis	1
Yin et al,[51] 2012	Systematic review and meta-analysis	1
Köninger et al,[52] 2008	Randomized controlled trial	1
Schnelldorfer et al,[53] 2006	Retrospective cohort study	4
Bramis et al,[54] 2012	Systematic review and meta-analysis	1
Kempeneers et al,[55] 2019	Systematic review and meta-analysis	1
Wu et al,[56] 2015	Systematic review and meta-analysis	1
Hamad et al,[75] 2018	Case series	4
Complications/sequelae		
Nikolic et al,[58] 2019	Systematic review	1
Malinka et al,[59] 2018	Case series	4
Chung et al,[60] 2016	Retrospective cohort study	3
Malka et al,[61] 1998	Case series	4
Zhu et al,[62] 2019	Systematic review and meta-analysis	1
Ni et al,[63] 2018	Retrospective cohort study	3
El Kurdi et al,[64] 2019	Systematic review and meta-analysis	1
Duggan et al,[65] 2014	Systematic review and meta-analysis	1
Vujasinovic et al,[66] 2021	Retrospective cohort study	3
Munigala et al,[67] 2022	Retrospective cohort study	3
Kirkegård et al,[68] 2017	Systematic review and meta-analysis	1
Gandhi et al,[69] 2022	Systematic review and meta-analysis	1
Ueda et al,[70] 2013	Prospective cohort	3
Pain		
Kuhlmann et al,[12] 2022	Case series	4
Phillips et al,[13] 2020	Case series	4
Olesen et al,[14] 2020	Case series	4
Olesen et al,[15] 2021	Randomized controlled trial	1
Kaufman et al,[16] 2010	Systematic literature review and meta-analysis	1
Baghdadi et al,[17] 2008	Systematic review	1
Issa et al,[18] 2015	Systematic review	1
Basinski et al,[19] 2005	Prospective, case-control study	3
Kwon et al,[34] 2016	Retrospective cohort study	3
Nutrition		
Martinez-Moneo et al,[20] 2016	Systematic review and meta-analysis	1
Olesen et al,[21] 2017	Cross-sectional study	4
Kuan et al,[22] 2021	Systematic review	1
de la Iglesia-Garcia et al,[23] 2017	Systematic review and meta-analysis	1
Czakó et al,[24] 2003	Prospective cohort study	2
Yaghoobi et al,[25] 2016	Systematic review and meta-analysis	1
Wiese et al,[26] 2021	Systematic review and meta-analysis	1
Rammohan et al,[27] 2015	Randomized controlled trial	1
Bhardwaj et al,[28] 2009	Randomized controlled trial	1
Zhou et al,[29] 2015	Systematic review and meta-analysis	1
Ahmed et al,[30] 2014	Systematic review and meta-analysis	1
Clinical guidelines		
Gardner et al,[71] 2020	Clinical guideline and systematic literature review	1
Conwell et al,[72] 2014	Clinical guideline/expert opinion	5

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Table 2. Diagnostic Performance of Imaging Modalities in the Diagnosis of Chronic Pancreatitis (CP)

Imaging modality	Sensitivity and specificity for CP, %[9]
Computed tomography	
Sensitivity	75
Specificity	91
MRCP	
Sensitivity	78
Specificity	96
EUS	
Sensitivity	81
Specificity	90
ERCP	
Sensitivity	82
Specificity	94

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography.

Because celiac plexus blocks have been shown to be as effective as the more invasive thoracoscopic splanchnicectomy, plexus blocks should be preferred if the intent is for short-term reduction of pain.[19] Patients with significant pulmonary morbidities, ie, prior intrathoracic operations such as lung resections or pleurodeses, may not be candidates for a thoracoscopic approach.

Nutrition

Seventeen percent of patients with CP have fat-soluble vitamin deficiencies,[20] 25% are underweight,[21] and 17% to 62% have sarcopenia.[22] As mentioned previously, there is no routine recommendation to routinely measure fecal elastase or fecal fat; however, enzyme replacement is indicated in patients with symptoms of exocrine insufficiency to improve fat and protein absorption and to improve gastrointestinal symptoms such as flatulence and steatorrhea. Enzyme replacement should be considered in all patients with CP experiencing symptoms of malabsorption or weight loss. Enzyme replacement clearly improves patient quality of life[23,24] but does not affect pain.[25] The data regarding pancreatic enzyme replacement impact on weight gain and mortality are inconclusive.[21,23,25]

Combination probiotics and prebiotics, or synbiotics, improve bowel frequency after 3 months of treatment, thereby improving QoL. Synbiotics may also lower total cholesterol and reduce infectious complications if administered in the perioperative period.[26,27] There are many studies investigating the role of antioxidant supplementation, but the results have been inconclusive.[28-30]

Endoscopy vs Surgery

In the Effect of Early Surgery vs Endoscopy-First Approach on Pain in Patients with Chronic Pancreatitis (ESCAPE) trial, 88 patients with CP who had dilated main pancreatic ducts were randomly assigned to 1 of 2 treatment pathways: endoscopic approach first or duodenal-preserving surgery first.[31] Results revealed that pain relief was achieved in 58% of patients who underwent early surgical intervention compared with 39% of patients who underwent endoscopy. Surgical patients had improved QoL and underwent less total interventions. In an earlier study, one-half of the patients randomly assigned to an endoscopy-first treatment arm ultimately underwent surgery.[32] There are no differences in preservation of endocrine or exocrine function whether patients undergo endoscopic interventions or surgery first.[33]

However, narcotic independence after ERCP and stenting also predicts narcotic independence after surgery.[34] Clinical improvement after ERCP or pancreatic duct stenting is not durable over the long-term given the short lifetime of these stents. Therefore, transient improvement with ERCP and pancreatic duct stenting may support a subsequent operative approach for a more durable improvement in symptoms, particularly pain.

Indications for surgery can be summarized as follows: symptomatic common bile duct stenosis or distortion, duodenal stenosis, vascular obstruction, refractory abdominal pain unresponsive to medical and endoscopic interventions, malnutrition, poor functional status or QoL due to symptoms, and suspicion of neoplasm. Pancreatoduodenectomy (PD) was the most common operation for CP before the development of duodenum-sparing techniques (**Table 3**, **Figures 2**A, B, C, and D). Surgery performed within 3 years from symptom onset as opposed to later in the disease course results in a greater likelihood of total pain resolution, less narcotic use, improved QoL, and lower rates of exocrine and endocrine insufficiency—without any differences in postoperative complications.[33,35-37] PD remains the operation of choice when malignancy is suspected.

It is well described that PD has high morbidity.[38] Izbicki et al[39] demonstrate that for patients with dilated ducts and inflammatory foci in the pancreatic head, operative time is significantly shorter, there are fewer postoperative complications (hemorrhage, fistulae, delayed gastric emptying), improved QoL, and superior pain relief after the Frey procedure compared with PD.[39] Subsequent studies corroborate most of these findings, but pain relief is variable.[40-44] In the Frey procedure (Figure 2B), the pancreatic head is cored out to remove the inflammatory focus, and a lateral pancreaticojejunostomy along the body and tail of the pancreas aids in drainage.

In the Beger procedure (Figure 2A), the pancreas is divided, and 2 anastomoses are created between the small bowel, proximal remaining portion of the pancreatic head, and the distal pancreatic body; in contrast, in the Frey procedure, the pancreatic head is cored out. The Berne procedure (Figure 2C), like the Frey method, involves coring out of the pancreatic head but without the extended lateral pancreatojejunostomy that is created in the Frey procedure. Unlike the Beger, Frey, and Berne operations, the Puestow procedure (Figure 2D) involves drainage only without pancreatic resection—a lateral pancreatojejunostomy is created without head resection or coring. Traditionally this is done only to the left of the gastroduodenal artery; however, extended lateral pancreatojejunostomies are also performed from the papilla to 1 cm from the tail.

Biliary diversion may be combined with any of the duodenal-preserving surgical methods when there is concern for common bile duct obstruction. This can be achieved through anastomosis directly to the small bowel or reimplantation into pancreatic resection cavity.

When the Beger procedure is compared with PD, there are short-term advantages in pain control and QoL, but these do not persist at longer-term follow-up. The Partial Pancreatoduodenectomy vs Duodenum-Preserving Pancreatic Head Resection in Chronic Pancreatitis (ChroPac) study, a multicenter, randomized, con-

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trolled, double-blind trial that randomly assigned 250 patients across 18 hospitals in Europe to treatment groups, compared PD with multiple organ-preserving operations (Beger, Frey, or Berne) and found no difference in QoL, pain, or pancreatic function.[42,45,46] The Cochrane Review concluded that additional randomized studies are required to draw any conclusions regarding improvement in QoL when comparing PD with duodenal-preserving operations.[47]

There are no differences in efficacy, mortality, exocrine or endocrine function, pain control, or QoL when comparing the Beger procedure with the Frey procedure.[48-51] Similarly, there are no differences in pain, QoL, or pancreatic function when comparing the Berne procedure with the Beger procedure, although the Berne modification requires less operative time.[48,52] The Puestow method is indicated only when there is not an inflammatory focus in the pancreatic head because it is purely a drainage procedure for dilated duct disease. If a patient fails to have adequate pain relief after the Beger, Frey, Puestow, or Berne procedures, it is unknown what the next best operative approach should be, prior to total pancreatectomy, and reoperations are more likely to have postoperative complications such as delayed gastric emptying and wound infections without clear improvement in symptoms.[53]

Total pancreatectomy with islet cell transplant is an absolute last resort for refractory CP, which involves removing the entire pancreas and reinjecting one's own acinar cells, most commonly into the portal vein. Total pancreatectomy is effective for pain control (79% have improved pain symptoms[54]) and for narcotic independence, which increases from an initial 0% to 15% range to 63% after surgery[55] but causes iatrogenic diabetes even with islet cell transplant (rates of insulin independence decrease from an initial 89% to 100% range to 30% 1 year after surgery).[54-56]

Prognosis

Median survival after CP diagnosis is 15 to 20 years due to complications from cardiovascular disease because diabetes, alcohol use, and smoking are risk factors for both processes.[57-59] Patients with CP are also more likely to develop visceral artery aneurysms and splenic complications such as splenic vein thrombosis, intracapsular hematoma, or rupture. In addition, patients with CP are 3 times more likely to develop a deep vein thrombosis and 4.5 times more likely to develop a pulmonary embolism compared with patients without CP.[60,61] Pancreatic-pleural fistulas occur, but they are exceptionally rare and account for less than 1% of all pleural effusions.

Fifteen percent of patients with CP develop diabetes within 36 months of diagnosis, which increases to 33% after 60 months.[62] Patients with endocrine and exocrine insufficiency are also more likely to develop small intestine bacterial overgrowth,[63,64] which may further worsen QoL, malnutrition, and difficulty with normal activities. Seventy-five percent of patients with CP develop osteoporosis or osteopenia,[65] and 44% with low bone marrow density sustain bony fractures.[66]

Patients with CP are at significantly higher risk of developing PDAC,[67] and are 4.28 times more likely than patients without pancreatic disease to develop PDAC 2 years from CP diagnosis. The risk persists but decreases to 3.14 at 10 years, likely due to initial diagnostic uncertainty.[68,69] Incidental cancer rates after resection for CP are as high as 7%,[59] but patients with CP who undergo surgery are less likely to develop cancer.[70]

Table 3. Surgical Options for Chronic Pancreatitis (CP)

Most suitable pathomorphology	Surgery	Description
Inflammatory focus in the pancreatic head, head mass, and/or carcinoma cannot be excluded. Chronic pancreatitis focus in the head	Pancreatoduodenectomy	The pancreatic head, pylorus, and duodenum are resected with creation of a gastrojejunostomy or duodenojejunostomy, pancreatojejunostomy and choledochojejunostomy or hepaticojejunostomy.
Inflammatory focus in the pancreatic head, normal duct	Beger	The pancreas is transected, and a resection of the pancreatic head is carried out with preservation of the duodenum and bile duct. Two anastomoses are created between the jejunum and pancreas—at the points of transection. The roux limb should measure between 45 to 50 cm.
Inflammatory focus in the pancreatic head, dilated duct	Frey	The head of the pancreas is cored out leaving a thin rim of tissue (avoiding transection and dissection above the portal and superior mesenteric veins) and a longitudinal pancreatojejunostomy along the pancreatic body is created with a roux limb of jejunum. The roux limb should measure between 45 to 50 cm.
Inflammatory focus in the pancreatic head, normal distal duct	Berne modification	The head of the pancreas is cored out with a single side-to-side anastomosis with the roux loop of jejunum. The roux limb should measure between 45 to 50 cm.
Normal head, dilated pancreatic duct >5 mm	Puestow	Drainage procedure sparing the pancreatic head. The main pancreatic duct is filleted open and longitudinal pancreatojejunostomy is created with a roux limb of jejunum and typically measures 45 to 50 cm.
Refractory CP, minimal change CP, failure of all other drainage procedures and medical management	Total pancreatectomy with Islet cell transplant	Resection of the entire pancreas is performed along with injection of one's own islet cells, typically into the portal vein, to engraft in the liver.

Discussion

The American College of Gastroenterology and the American Pancreatic Association recommend a stepwise approach to both diagnosis and treatment of CP.[71,72] A comprehensive patient history including an evaluation of environmental and familial risk factors, presence of diabetes, signs and symptoms of malnutrition and/or maldigestion, weight loss, a personal history of autoimmune disorders, and a thorough oncologic history must be obtained.

CT or MRI should be the first-line imaging modalities for diagnosis; EUS should be considered as a second-line approach or to compliment cross-sectional imaging in order to obtain biopsies if a cancer diagnosis is in question. ERCP does not visualize the parenchymal architecture and is also invasive; therefore, although it may be both a diagnostic and therapeutic modality, it should not be used alone.

Treatment begins with the least invasive but most challenging intervention: alcohol and smoking cessation and nutritional

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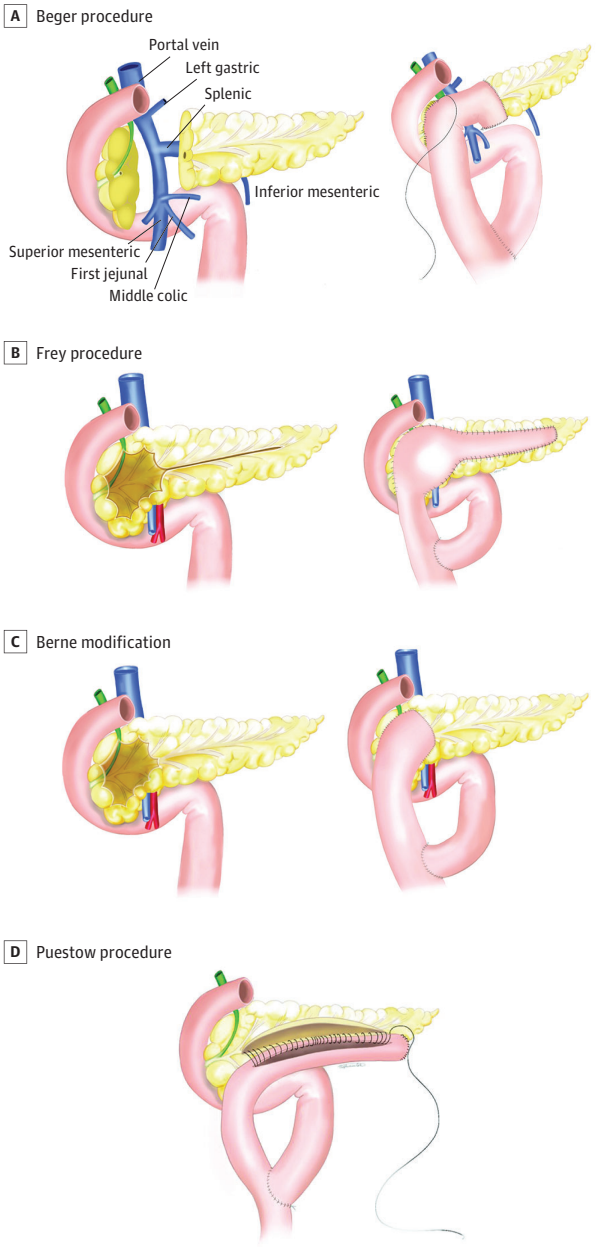
Figure 2. Duodenum-Sparing Techniques



Duodenum-sparing techniques include the Beger procedure (A), Frey procedure (B), Berne modification (C), and the Puestow procedure (D).

optimization. Enzyme supplementation does not improve CP pain per se but should be prescribed for any patient with symptoms of malabsorption to improve nutritional status and to decrease gas pain, bloating, and gastrointestinal discomfort. Understanding patients' pain severity remains elusive, and pain management for CP varies widely between institutions and individual clinicians.

Interdisciplinary treatment combining behavioral approaches to pain management, psychiatric evaluation and treatment for depression, anxiety, and addiction in combination with medical and surgical management is more effective and lowers overall health care costs.[73] A step-up approach should be taken for analgesia, beginning with nonnarcotic medications such as acetaminophen, NSAIDs, pregabalin, antidepressants, weak opioids, and strong opioids. The data regarding the effectiveness of celiac plexus block and thoracoscopic splanchnicectomy suggest that these modalities may be effective as a bridge to surgery because their effects are largely temporary.

Although surgical decompression has better long-term outcomes compared with endoscopic therapies, it is reasonable to first trial less invasive options such as ERCP with sphincterotomy, stenting, stricture dilation, and/or stone extraction, reserving surgical drainage or resection for treatment failure, at least within the first 3 years of symptom onset and while patients still have a reasonable QoL.

When surgery is indicated, duodenal-preserving choices (Beger, Frey, Puestow, and Berne) are preferred to some extent over classic and pylorus-preserving PD, unless cancer is suspected. However, preferences vary somewhat geographically.[74] Surgeon experience, practice, and level of comfort likely also affect operative choice. The Frey and Berne operations avoid both transecting the pancreas and the technically demanding dissection near the portal and superior mesenteric veins as required by the Beger procedure, and yet they have equivalent outcomes. Furthermore, laparoscopic and robotic surgery is gaining popularity and is used for all forms of pancreatic resections, drainage procedures, and for total pancreatectomies,[75] which may affect the ease of dissection and anastomosis and the surgeon preference for specific operations. In addition, the postoperative outcomes may be modified.

There are currently no recommendations for routine cancer screening in patients with CP without an established familial component; however, patients with CP are at a substantially higher risk for cancer compared with the general population, especially in the first few years after diagnosis.[68,69] Delay in diagnosis of PDAC could prevent or delay curative resection. This issue impacts decision-making for surgical intervention when there is a mass suspected to be malignant.

Much is still ambiguous regarding the management of CP. The literature supports that early surgery, within 3 years from symptom onset, is superior to delayed surgery, but it remains unclear when one should forego endoscopic interventions and proceed directly to surgery, and these interventions are decided on in a case-by-case basis with substantial variation from center to center depending on local expertise and resources. Additional research is required to determine if thoracoscopic splanchnicectomy or celiac plexus blocks are effective as the current data are heterogeneous. Current nutrition guidelines require standardization; implementation of nutritional support is often limited by resource constraints especially in the outpatient setting.

Limitations

Limitations of this review include its broad exclusion criteria. Many publications were excluded on a subjective basis that more clinically relevant or higher level–evidence publications on the same topic were also available.

Conclusions

Results of this systematic review reveal that patients with CP require multidisciplinary and multimodal treatment. Early surgical

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intervention leads to improved pain symptoms, but type of surgery, when to offer endoscopic vs surgical interventions, and strategies for nutritional optimization require further investigation.

ARTICLE INFORMATION

Accepted for Publication: January 21, 2023.

Published Online: April 19, 2023. doi:10.1001/jamasurg.2023.0367

Author Contributions: Drs Cohen and Kent had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Cohen.
Administrative, technical, or material support: All authors.
Supervision: Kent.

Conflict of Interest Disclosures: None reported.

Additional Information: All figures are original. Illustrations in Figure 2 were created as original work by Stephanie M. Cohen, MD (first author).

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