Management of Chronic Pancreatitis

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Advances in our understanding of chronic pancreatitis have improved our care of patients with this disease. Although our therapies are imperfect and many patients remain symptomatic, appropriate medical care improves the quality of life in these patients. Proper management requires an accurate diagnosis, recognition of the modifiable causes of disease, assessment of symptoms and complications, treatment of these symptoms and complications utilizing a multidisciplinary team, and ongoing monitoring for the effect of therapy and the occurrence of complications.

Keywords: Chronic; Pancreatitis; Management.

Chronic pancreatitis is a syndrome characterized by inflammation, fibrosis, and loss of acinar and islet cells. The syndrome can produce symptoms (pain) and, with sufficient tissue destruction, exocrine or endocrine insufficiency. Not all patients with chronic pancreatitis develop symptoms or exocrine or endocrine insufficiency. Disease progression often begins with an early phase that is characterized by episodes of abdominal pain and can be mistaken for acute pancreatitis. In this phase, clear-cut evidence of chronic pancreatitis can be lacking. With time, pain can become more persistent and severe, imaging tests can show evidence of chronic pancreatitis, and exocrine and endocrine insufficiency might develop. This process can take many years.[1] Although chronic pancreatitis seems to first require acute pancreatitis, most patients with acute pancreatitis of various etiologies do not go on to develop chronic pancreatitis[2]; the risk of progression to chronic disease is greatest among patients who smoke or have had alcohol-related acute pancreatitis.

The management of chronic pancreatitis is challenging, and most patients remain symptomatic despite therapy. There are no effective methods to stop progression or reverse this syndrome. However, a number of new insights have improved therapy and provided some evidence based on which therapy to choose.

Proper management of chronic pancreatitis starts with an accurate diagnosis. This is often challenging for patients with early-stage disease, who do not always have definitive evidence of chronic pancreatitis. Next, it is important to determine etiologic agents that contribute to disease so that these can be addressed if possible. Individualized treatment of symptoms and exocrine and endocrine insufficiency is necessary, because patients have variable expression of disease. Finally, ongoing monitoring provides opportunities to detect complications at earlier stages so that more effective therapy is possible. Optimal management of these patients requires a multidisciplinary team that includes gastroenterologists, surgeons, endocrinologists, dieticians, pain management, psychiatrists, social workers, and patient support groups.

Diagnosis

Chronic pancreatitis is usually diagnosed based on results of imaging analyses or tests of pancreatic function. Although histologic evidence of fibrosis and tissue loss might be considered the most definitive diagnostic criteria, it is rarely available. In addition, similar changes in histologic features are observed in patients without symptoms of chronic pancreatitis, such as very elderly patients, those with diabetes or renal failure, and those who smoke. These changes can result from normal "wear and tear" on the pancreas. Diagnosis requires recognition of the variety of symptoms (if present) and complications that constitute the syndrome,[3] in conjunction with appropriate imaging or functional tests (Table 1). In early stages of disease progression, results from these tests can be negative or inconclusive. In later stages, marked changes in pancreatic structure and function make diagnosis much

Abbreviations used in this paper: CT, computed tomography; DPPHR, duodenum-preserving pancreatic head resection; ERCP, endoscopic retrograde cholangiopancreatography; ESWL, extracorporeal shock wave lithotripsy; EUS, endoscopic ultrasonography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; TIGAR-O, Toxic-Metabolic, Idiopathic, Genetic, Autoimmune, Recurrent and Severe Acute Pancreatitis, Obstructive.

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Table 1. Diagnostic Tests for Chronic Pancreatitis

Imaging tests	
EUS	Two systems of reporting are used: standard terminology and Rosemont criteria.[5] EUS allows detailed examination of both the pancreatic parenchyma and the pancreatic duct.
MRI with MRCP	Administration of secretin during MRCP improves the quality of imaging of the pancreatic duct and may allow the pancreatic secretory capacity to be estimated. MRI cannot visualize calcification.
CT	CT images the pancreatic parenchyma well, with less ductal detail than MRI.
ERCP	ERCP provides the most detailed images of the pancreatic duct but is rarely used for diagnosis.
Ultrasonography	Ultrasonography has limited ability to image the pancreas, but it is of low cost and has no ionizing radiation.
Functional tests	
Secretin test	Administration of a supraphysiologic dose of secretin produces maximal pancreatic stimulation; pancreatic juice is collected with a Dreiling tube or an endoscope and analyzed for bicarbonate concentration.
Fecal elastase	Low levels in the stool (<200 μg/g of stool) are seen in patients with advanced chronic pancreatitis.
Serum trypsin	Low levels (<20 mg/dL) are seen in patients with advanced chronic pancreatitis.

easier and more accurate. Of course, at this later stage, there is less opportunity to interrupt disease progression.

Accurate diagnosis is therefore especially important during the early stages of disease. Patients arrive at many pancreas specialty clinics with a chronic abdominal pain syndrome and normal results from pancreatic imaging tests, yet they have been incorrectly diagnosed with chronic pancreatitis and may have been subjected to dangerous and ultimately futile interventions, such as endoscopic retrograde cholangiopancreatography (ERCP) with stent placement or prescriptions for narcotics.

Characteristic findings from imaging techniques such as computed tomography (CT) or ultrasonography include atrophy of the pancreas, a dilated pancreatic duct, and pancreatic calcifications (Figure 1). These features are pathognomonic of chronic pancreatitis and can take 5 to 10 years or more to develop.[1] Pancreatic calcifications seem to be much more common in patients with certain forms of chronic pancreatitis, especially those with hereditary pancreatitis (caused by variants of *PRSS1*), patients who smoke or drink alcohol, or patients with tropical pancreatitis. Patients with chronic pancreatitis of other etiologies can also develop calcifications, detected by imaging tests, although these are observed less frequently and develop more slowly.

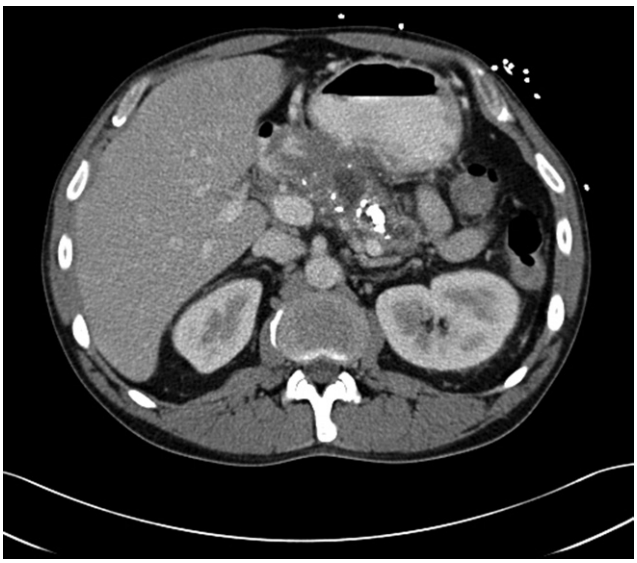

Figure 1. CT scan shows a dilated pancreatic duct and a large pancreatic calcification.

Additional methods to image the pancreas include magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP, with or without the secretagogue secretin), endoscopic ultrasonography (EUS), and ERCP. MRI with MRCP has replaced CT at many institutions. One advantage of MRI is that it can be used to characterize the pancreatic ductal anatomy (with MRCP), but it often misses calcifications. Administration of secretin during MRCP improves the quality of images of the pancreatic duct, although the gain in diagnostic accuracy with this technique has not been defined. In addition, the quantity of pancreatic secretions can be estimated using MRI with secretin.[4]

EUS allows for detailed imaging of the pancreatic duct and parenchyma (Figure 2). EUS images can be interpreted using the traditional 9-feature scheme or the newly proposed Rosemont criteria.[5] These systems do not appear to differ in diagnostic accuracy for chronic pancreatitis. However, it is important to recognize that subtle abnormalities detected by EUS are nonspecific and not sufficient for diagnosis of chronic pancreatitis. EUS has a high level of sensitivity and a low level of specificity.

Imaging techniques such as CT, MRI, and EUS can also be used to exclude other conditions that produce similar symptoms to, or complicate, chronic pancreatitis, especially pancreatic ductal adenocarcinoma, intraductal papillary mucinous neoplasm, and other cystic neoplasms. Although ERCP provides detailed images of the pancreatic duct, it is not appropriate for use in diagnosis of chronic pancreatitis, although it might be used therapeutically.

Biochemical tests of pancreatic function are used much less commonly than imaging analyses. In a direct test of pancreatic function, patients are given an infusion of the hormone secretin, and pancreatic secretions are collected and analyzed for bicarbonate concentrations; pancreatic juice is collected using a Dreiling tube or an endoscope. Although there is evidence that this test can detect

Figure 2. EUS image shows subtle sonographic features of chronic pancreatitis, with a hyperechoic duct margin and hyperechoic foci in the gland. These features are nonspecific and cannot be used alone to diagnose chronic pancreatitis.

chronic pancreatitis at earlier stages than imaging studies, it is only performed at a few centers and is not available to most patients. Indirect assessment of pancreatic function using tests such as fecal elastase is also possible but not accurate for diagnosis. A diagnostic algorithm has been recently proposed[6] that first uses commonly available tests (CT, MRI, and EUS) and reserves direct tests of pancreatic function to clarify equivocal results (Supplementary Figure 1).

Analysis of the fluid collected during a direct pancreatic function test, in addition to bicarbonate concentration, can allow additional insights into mechanisms of disease and identify new diagnostic tools. Differentially expressed proteins can be identified in pancreatic secretions from patients with chronic pancreatitis compared with patients with nonpancreatic pain.[7] These proteins include many involved in inflammation, fibrosis, and pain. Similar analyses are possible in patients with malignant or premalignant pancreatic disease. Whether these approaches will evolve to accurate diagnostic tests in early chronic pancreatitis is not yet known.

Determination of Etiology

In the past, alcohol consumption was believed to cause most cases of chronic pancreatitis. Recent evidence indicates that although alcohol contributes significantly to pathogenesis, it is not the main cause of disease for most patients. The Toxic-Metabolic, Idiopathic, Genetic, Autoimmune, Recurrent and Severe Acute Pancreatitis, Obstructive (TIGAR-O) classification system[8] categorizes known causes and factors that contribute to chronic pancreatitis (Supplementary Table 1). Determining disease etiology(s) provides opportunities for focused and specific treatments, such as corticosteroids for patients with autoimmune pancreatitis, relief of duct obstructions for patients with chronic ductal strictures, and lifestyle modifications (abstinence) to slow disease progression and preserve pancreatic tissue.

Long-term ingestion of large quantities of alcohol (on average, >5 drinks per day) is required for development of alcohol-associated chronic pancreatitis. Smoking appears to be an equally injurious toxin. Continued alcohol use or smoking accelerates the progression of chronic pancreatitis and the development of pancreatic calcifications and also increases the risk of pancreatic and nonpancreatic malignancy. Physicians should make vigorous efforts to encourage sustained abstinence for patients with chronic pancreatitis as early in the clinical course of disease as possible. A randomized trial showed that even simple interventions (a 30-minute discussion), delivered in a repeated and systematic way, helped patients abstain from alcohol and reduced recurrence of pancreatitis.[9] Because many gastroenterologists may not have the expertise or experience to provide support for smoking cessation and alcohol abstinence, referral of patients to appropriate support groups should be consistently provided.

Treatment of Pain

Most patients with chronic pancreatitis have abdominal pain. Pain takes many forms; a common presentation is a chronic and continuous pain, with or without exacerbations. Pain severity, character, timing, and response to therapy vary. Pain can change over time in individual patients and in some patients can eventually disappear. Pain can develop during early stages of chronic pancreatitis, before development of easily visible structural abnormalities of the pancreas. In this situation, it can be difficult to determine if pain is actually caused by chronic pancreatitis. Pain is the symptom that most frequently causes patients to seek medical care; it accounts for most chronic pancreatitis–associated medical costs and causes the greatest reductions in social function and quality of life. Recent studies have found that certain pain patterns are most detrimental to quality of life. Continuous pain, even if less intense than intermittent pain, is associated with a lower quality of life, increased disability, and greater health care utilization.[10] It is helpful to quantify pain severity and character, determine baseline levels of pain, and measure the effects of therapies. Some assessment of quality of life and disability is also appropriate on a periodic basis.

In the past, pain was believed to be mainly caused by obstruction of the pancreatic duct (by stricture or stone), which results in high pressure or ischemia above the obstruction. Therapies that relieve the obstruction, such as ERCP with stent placement or surgical ductal drainage, were therefore used to treat pain. Although this approach has been successful in some patients, its effects are un-

predictable. Of course, patients with early-stage disease can have severe pain without any evidence of ductal obstruction, and patients with a stone or stricture causing duct obstruction may have no pain.

More recent studies have moved beyond this simple "plumbing" viewpoint of pathophysiology. The pancreas contains many nociceptive neurons. In patients with chronic pancreatitis, these neurons are increased in size and often surrounded by inflammatory infiltrates. In addition to the usual stimuli that cause pain (ischemia, heat, inflammation), the pancreatic enzyme trypsin strongly activates these nociceptors. The primary nociceptive neurons communicate with second-order neurons in the spinal cord, which can develop abnormal function and become sensitized. Sensitization produces hyperalgesia (a magnified pain response to nociceptive stimuli) and allodynia (a pain response to a normal physiologic stimulus). These second-order neurons communicate with third-order neurons in the brain, which connect to the limbic system and somatosensory cortex; this causes the physical sensation of pain and the emotional response (suffering) caused by pain.

There are significant changes in brain function, microstructure, and macrostructure in patients with painful chronic pancreatitis, producing changes in electroencephalography patterns, brain-evoked potentials, and cortical organization and thickness. These changes are similar to those observed in patients with other conditions that cause chronic visceral or somatic pain. These changes in nociception indicate that pancreatitis-related pain could be primarily a "wiring" problem, rather than a plumbing problem, that would not respond to treatments that simply remove ductal obstructions.[11] These changes could account for the benefits of agents such as gabapentoids in reducing pain in patients with chronic pancreatitis.[12] Their effects are likely to result from their abilities to modulate nociception. Finally, it is worth noting that the placebo response in these patients is at least 20%.

The first step in treating pain is to search for treatable complications of chronic pancreatitis. These could include a pancreatic pseudocyst, obstruction of a surrounding hollow viscus (bile duct or duodenum), or cancer. Although these complications do not always cause pain, they do have specific treatments. Cross-sectional imaging with CT or MRI can be used to identify complications and screen for conditions that produce symptoms that are similar to those of chronic pancreatitis (pancreatic adenocarcinoma or intraductal papillary mucinous neoplasm).

Pain treatment begins with medical therapy. One important goal of effective medical therapy is to slow disease progression, which involves focused efforts to achieve abstinence from tobacco and alcohol if they have roles in disease development. Alcohol abstinence usually reduces pain, although the magnitude of the effect is unpredictable. More importantly, abstinence slows disease progression, reduces the likelihood of complications such as carcinomas, and prolongs life.[13]

Most patients with pain will require analgesics. Cross-sectional and cohort studies estimate that approximately half of all patients with chronic pancreatitis will be treated with opioids. The precise risk of addiction is not known, but studies of patients with other chronic pain syndromes indicate that it is less than 20%. Patients with previous addictive behaviors, including alcohol abuse or smoking, are most prone to dependence, abuse, or addiction; the rate of addiction and other aberrant drug-related behaviors thus varies among patients with chronic pancreatitis.

Notwithstanding the risk of addiction, the main goal is pain relief. It is appropriate to begin treatment with less-potent opioids. Tramadol is commonly used for this purpose in dosages of 200 to 400 mg daily, although higher dosages are given to some patients. More potent narcotics are often required, and it is appropriate to slowly increase potency and frequency, with a goal of reducing but not eliminating pain. A number of other agents are given with opioids to manage chronic pain syndromes. These include tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and gabapentoids. Of these, only pregabalin has been studied in a randomized controlled trial in patients with chronic pancreatitis.[12] Patients treated with pregabalin (up to 300 mg twice daily) had reduced pain compared with those given placebo and were able to reduce opioid use. Side effects were more common in the pregabalin group (lightheadedness or a feeling of being drunk). Preliminary studies suggest that pregabalin inhibits central sensitization. It is not clear whether other adjunct agents are equally effective or if combinations of these agents are more effective. Nonetheless, use of adjuvant agents is reasonable for patients who require opioids for pain control.

Additional medical options for pain include administration of pancreatic enzymes, octreotide, antioxidants, and various nontraditional therapies. Pancreatic enzymes have been studied in 7 small randomized trials with crossover designs, with mixed results. These studies had significant heterogeneity in patient selection, enzyme dosage and formulation, and outcome measures.[14] Octreotide has been studied in 4 randomized trials with mixed results and is rarely used. Although enzyme therapy may not provide substantial benefit, it is often tried because of its safety and the lack of other highly effective treatments.

The effects of antioxidants were tested in 2 relatively large randomized trials.[15,16] Although serum levels of antioxidants increased in both trials, they produced different results for the outcome of pain relief. The trials included different types of patients; the trial with the positive results included much younger patients with mainly idiopathic pancreatitis, whereas the trial that produced negative results included older patients with alcohol and smoking as the primary etiologies.[17] Antioxidants might reduce pain, but further studies are needed to define the patient population most likely to respond.

Patients with chronic pancreatitis should be educated about healthy lifestyle choices. They have increased risks of osteoporosis, osteopenia, and fractures,[18] so periodic assessments of bone density and vitamin D levels as well as routine dietary supplementation with vitamin D and calcium are recommended.

There is one form of chronic pancreatitis that has specific medical therapy. Autoimmune pancreatitis occurs in 2 forms.[19] Type 1 is characterized by the presence of immunoglobulin G4–positive plasma cells in affected organs, and some patients have increased serum levels of immunoglobulin G4. The most common presentation is obstructive jaundice, but a variety of organs can be involved, including salivary glands, bile ducts, kidneys, and lungs. Type 2 is not associated with altered levels of immunoglobulin G4 and involves only the pancreas. Both types of autoimmune pancreatitis respond to corticosteroid therapy, although relapse can occur and require other immunosuppressive therapies. Corticosteroid therapy, if promptly initiated, may prevent the development of exocrine or endocrine insufficiency.

For patients who do not respond to medical therapy, options include endoscopic therapy, nerve block or neurolysis, and surgery. Endoscopic therapy aims to remove obstructions (strictures or stones) in the main pancreatic duct. This approach requires careful patient selection and detailed evaluation of pancreatic duct anatomy. Duct anatomies that are most amenable to endoscopic therapy include a dilated main pancreatic duct (usually more than 5–6 mm) with an obstructing stone in the head or a ductal stricture in the head. It is not clear what proportion of patients with chronic pancreatitis has ductal anatomy that is amenable to endoscopic therapy but is certainly far less than half. It is essential to rule out cancer before treating an isolated pancreatic duct stricture. In patients with multiple stones or impacted stones, endoscopic therapy is more challenging and less effective. It should be noted that ductal abnormalities such as dilatation and stones do not correlate with symptoms. Furthermore, changes in duct diameter after endoscopic therapy (effective duct decompression should theoretically reduce duct diameter) do not correlate with relief of symptoms.

Endoscopic therapy comprises pancreatic and biliary sphincterotomy, stricture dilation and stenting, stone extraction, and lithotripsy. Stones and strictures that are too far from the ampulla are usually not amenable to endoscopic therapy. Large stones or impacted stones usually require extracorporeal shock wave lithotripsy (ESWL) or intraductal lithotripsy; these techniques apply shock waves to break up stones.

A number of large retrospective studies have evaluated the efficacy of endoscopic therapy for painful chronic pancreatitis. A retrospective analysis of 1000 patients treated with a variety of techniques, including ESWL, found that endoscopic therapy was technically successful for 69% of patients, with lower rates of success associated with more complex ductal anatomies.[20] After a mean period of 4.9 years, 66% of patients were pain-free, with another 19% reporting mild pain. Approximately 25% of patients underwent surgery, generally for failure of pain relief after endoscopic therapy. A separate retrospective analysis of 146 patients found that approximately 50% of patients who received endoscopic therapy had pain relief and that half of the nonresponders required surgery for their pain.[21] Pain was also reduced in approximately 33% of patients who received only medical therapy.

Because these were retrospective studies, which did not use standardized or validated measures to assess response, they can only estimate the effectiveness of endoscopic therapy. Nonetheless, it appears that endoscopic therapy is technically successful (approximately 80%) for carefully selected patients with appropriate ductal anatomy and that 50% to 70% of these patients have some pain relief.

Lithotripsy is necessary as an adjunct to endoscopic therapy for many patients with pancreatic duct stones. Interestingly, a randomized trial compared ESWL alone with ESWL followed by ERCP in removal of pancreatic duct stones.[22] Pain relief was equivalent between groups, and there were significant cost savings for the group that did not receive ERCP. These findings indicate that breaking up obstructing stones could be sufficient to improve ductal drainage and relieve pain. However, an alternative explanation is that lithotripsy reduces pain by a mechanism other than fracturing stones, perhaps by changing nociception through some effect on intrapancreatic nerves.

Another endoscopic treatment option is nerve block or neurolysis with EUS. Neurolysis delivered by EUS guidance is safer and more effective than CT-guided techniques. EUS-guided delivery of bupivacaine and corticosteroids to block nerves has limited effectiveness in patients with chronic pancreatitis. Approximately 50% of patients have pain relief with a duration of a few weeks, so this approach is not recommended for patients with chronic pancreatitis. It is more effective for patients with pain from pancreatic cancer who have not developed sensitization. Neurolysis with injection of absolute alcohol is not recommended for patients with painful chronic pancreatitis. Neurolysis with thoracosocopic splanchnicectomy is rarely used for patients with chronic pancreatitis and its effectiveness is limited, similar to the EUS-guided nerve block.

Surgical therapy is considered for patients who have not responded to medical or endoscopic therapy. Surgery is appropriate for pain, local complications such as duodenal or biliary obstruction, and when cancer is suspected but cannot be excluded in preoperative evaluations. A variety of surgical options are available. Selecting the appropriate surgical approach requires analysis of pancreatic ductal anatomy, consideration of local complications such as duodenal or bile duct compression, and assessments of available surgical expertise. The most commonly performed procedure is the lateral pancreaticojejunostomy or modified Puestow operation. This involves a longitudinal incision of the anterior pancreas and pancreatic duct. The incision usually extends from near the

pancreatic tail to as close to the duodenum as is feasible. Ductal stones are removed and strictures are incised, and the incision is overlaid with a defunctionalized roux limb. This operation requires a dilated pancreatic duct (usually more than 6 mm in diameter). Approximately 80% of patients have pain relief immediately after this operation, but only approximately 50% still have pain relief 5 or more years after follow-up.

Several surgical approaches involve drainage of the pancreatic duct along with localized resection of the pancreatic head, forms of a duodenum-preserving pancreatic head resection (DPPHR) or a pancreaticoduodenectomy (Whipple operation). These procedures are most frequently considered for patients with an inflammatory mass of the pancreatic head, often with associated obstruction of the bile duct or duodenum. Several randomized controlled trials reported a similar effect on pain following these operations but found that the Whipple procedure was more frequently associated with postoperative diabetes and lower quality of life.[23,24] There are 3 forms of DPPHR: the Frey, Beger, and Berne operations. These appear to be equally efficacious, and selection depends on local surgical expertise. Short-term pain relief from these operations appears equivalent to that from the modified Puestow operation. Long-term pain relief appears to be better.[24] Patients who undergo DPPHR frequently develop exocrine and endocrine insufficiency as consequences of the surgical resection and continued pancreatitis in the remnant pancreas.

Distal pancreatectomy, with resection of the pancreatic tail, is rarely performed but can be appropriate for patients with disease limited to the pancreatic tail (such as ductal stricture from trauma, with obstructive chronic pancreatitis in the tail). Patients with a nondilated pancreatic duct can be treated with a variation on the modified Puestow operation, in which a V-shaped incision is made in the anterior surface of the pancreas to include the nondilated pancreatic duct; this is overlaid with a Roux limb. This procedure, called a V-plasty or Hamburg procedure, is performed mainly in Europe.

Total pancreatectomy is also rarely performed and can be coupled with autotransplantation of islet cells. In this procedure, the resected pancreas is digested, and the islets are collected and infused into the portal vein; they implant in the liver and reduce the severity of diabetes after pancreatectomy. This operation has been considered a last resort for patients who have failed to respond to previous surgical therapies, although it is increasingly considered for patients who have not undergone surgery. Pain relief occurs in approximately 66% of patients after total pancreatectomy, indicating the complex extrapancreatic mechanisms of pain.[25,26] A study reported that 45% of patients who underwent this procedure were initially insulin independent after surgery, although insulin independence decreased over time.[25] The risk of diabetes was inversely related to islet cell yield from the resected pancreas, and previous pancreatic drainage procedures (such as the modified Puestow operation) seemed to reduce yield. It is not clear whether this reduction in yield resulted from difficulties in digesting the pancreas to obtain islets following the modified Puestow operation or from the patients' stage of disease (more advanced disease with fewer residual surviving islets at the time of total pancreatectomy). Patients must be carefully selected for total pancreatectomy with autotransplantation of islets so, for the moment, it is a last resort.

Two trials have compared endoscopic and surgical therapies for pain from chronic pancreatitis. The first included 72 patients treated with endoscopy (comprising sphincterotomy, stricture dilation and stenting, and stone extraction with lithotripsy if necessary) or surgery (simple drainage or DPPHR and Whipple operations).[27] One year later, pain relief was equivalent between groups. After 5 years, 34% of the surgery group and 15% of the endoscopy group still had complete relief of pain. Partial relief of pain was equivalent between groups (approximately 50%).

A trial of 39 patients was stopped early because patients in the surgery group had significant improvements in outcome.[28] After a median follow-up period of 24 months, 75% of patients in the surgery group and 32% in the endoscopy group had complete or partial relief of pain. Five years later, 68% of patients in the endoscopy group underwent surgery, which remained superior in providing pain relief.[29] Costs, quality of life, and pancreatic function were equivalent in the follow-up analysis.

These trials included patients with ductal anatomies that were amenable to endoscopic or surgical therapy. They primarily included patients with a dilated pancreatic duct and an obstructing stone or stricture. For these patients, surgery appears to be somewhat more effective and more durable than endoscopic therapy.[30] These results are appropriate to discuss with patients, many of whom will still opt for endoscopic therapy out of a desire to avoid surgery.

The treatment of pain remains the most difficult challenge in managing patients with chronic pancreatitis.[17] Medical therapy is appropriate for all patients, and pain can be reduced to a manageable level in many. Endoscopy and surgery are options for select patients. An algorithm outlining a reasonable approach is presented (Figure 3).

Management of Exocrine Insufficiency

Exocrine insufficiency most commonly develops after 5 to 10 years of chronic pancreatitis but can also develop in patients with other pancreatic disorders (Supplementary Table 2). Exocrine insufficiency should be suspected in patients with these conditions who have clinical features of or laboratory test results that suggest malabsorption. These include diarrhea, steatorrhea, weight loss, metabolic bone disease, or vitamin or mineral deficiency. Exocrine insufficiency is not identified in many patients who have it, and many who are diagnosed with exocrine insufficiency are undertreated. A 72-hour analysis of fecal fat concentrations on a high-fat diet is necessary to identify steatorrhea, but this test is rarely per-

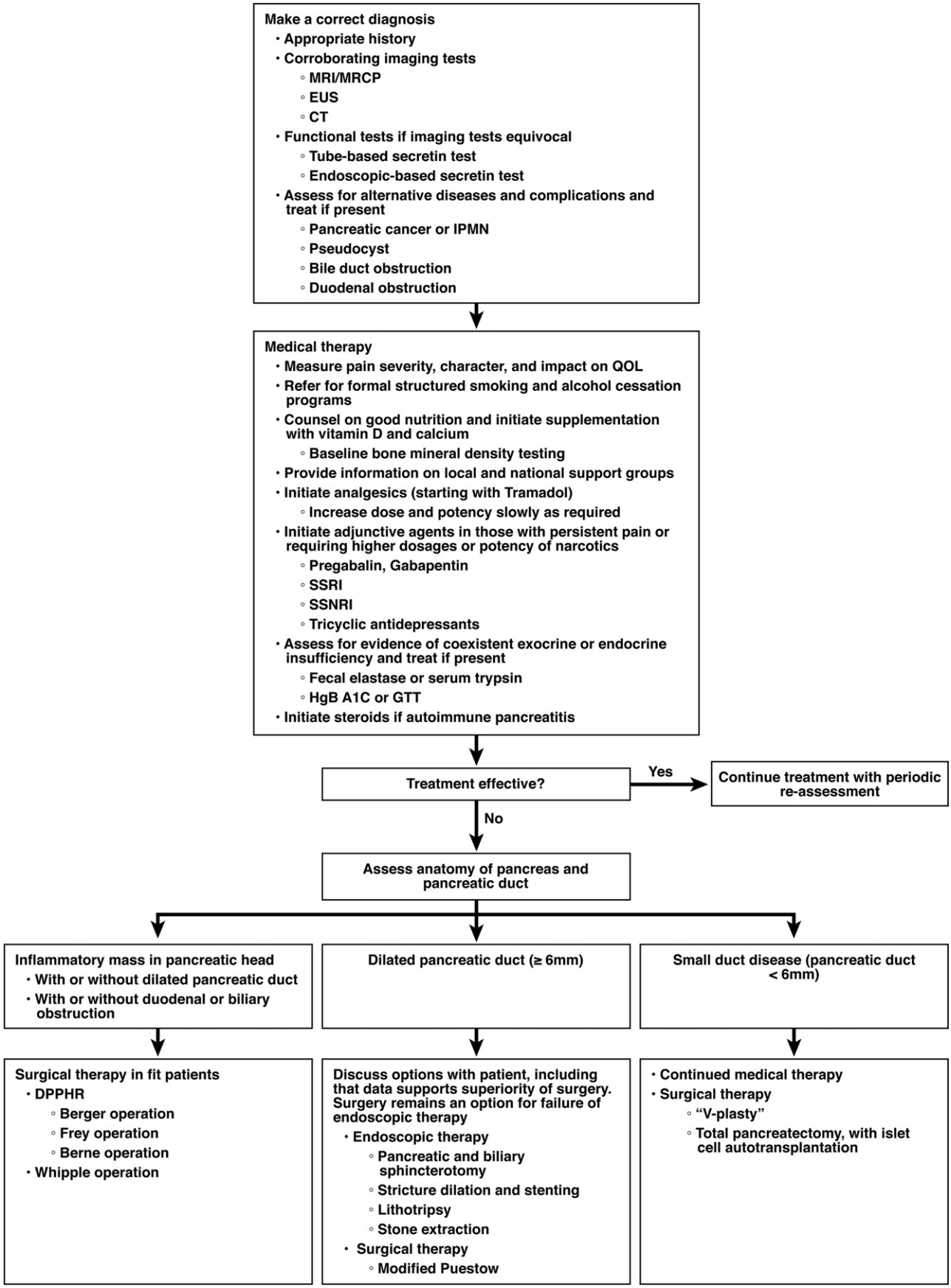

Figure 3. Management algorithm for chronic pancreatitis. IPMN, intraductal papillary mucinous neoplasm; QOL, quality of life; SSRI, selective serotonin reuptake inhibitor; SSNRI, serotonin-norepinephrine reuptake inhibitor; GTT, glucose tolerance test.

formed. Low levels of fecal elastase (<200 μg/g stool) or serum trypsin (<20 ng/mL) are usually observed in patients with exocrine insufficiency and can confirm the typical clinical signs of this disorder.

A baseline evaluation of nutritional status is appropriate when patients begin pancreatic enzyme therapy. Patients' weight and body mass index should be determined, and basic laboratory tests should be performed, including complete blood counts (with differential), comprehensive metabolic panel, international normalized ratio, and levels of albumin, prealbumin, carotene, and vitamin D. Bone mineral density testing is also appropriate.

Treatment of exocrine insufficiency requires pancreatic enzyme replacement. It is estimated that the healthy human pancreas produces 900,000 USP units of lipase with each meal and that approximately 10% of this amount is necessary to achieve relatively normal absorption of fat and fat-soluble vitamins. In the past, there was confusion about this estimate, because 2 different systems were used to measure the lipase content of products (IU and USP units). Enzymes are sold in the United States by USP unit. Approximately 90,000 USP units of lipase per meal are needed for appropriate fat absorption. In many patients, the pancreas still produces some lipase, or there are compensatory increases in secretion of gastric lipase, so the full 90,000 USP units per meal is always not required. Nonetheless, studies from several countries have found that many patients do not receive sufficient amounts of enzymes. A number of agents are available (Table 2). Most are enteric-coated microsphere capsules, but one is in tablet form and is not enteric coated. Lipase is sensitive to degradation by acid, so the nonenteric product requires cotreatment with an agent to suppress gastric acid, such as an H_2-blocker or proton pump inhibitor.

Although pancreatic exocrine insufficiency can interfere with digestion of fats, proteins, and carbohydrates, the effect is most pronounced on fat and fat-soluble vitamin absorption. It is appropriate to begin therapy with at least 40,000 to 50,000 USP units of lipase with each meal and half that amount with snacks. The enzymes should be taken during and after the meal; splitting the doses between these times is commonly recommended. The dose of enzymes can be adjusted based on their effects (reductions in diarrhea or steatorrhea, weight gain) and by increases in levels of fat-soluble vitamins and nutritional measures. If there is evidence of an insufficient response, the dosage can be increased up to 90,000 USP units of lipase with each meal and occasionally more. Supplementation with fat-soluble vitamins is also appropriate.

There are quantitative methods to determine the efficacy of fat absorption, including a 72-hour fecal fat measurement and breath tests, but these are rarely performed outside of clinical research studies. Pancreatic enzyme therapy can be ineffective because of inadequate dose administration, asynchrony in delivery of enzymes and food simultaneously to the intestine (especially in patients who have undergone pancreatic surgery), or acid inactivation of lipase. Non–enteric-coated preparations require coadministration with acid-reducing agents, but these can also increase the efficacy of enteric-coated preparations. Acid-reducing agents allow enteric-coated enzymes to be released from their pH-sensitive delivery system more proximally in the duodenum, the site of most normal fat and fat-soluble vitamin absorption.[31] Continued failure of therapy despite an adequate dose and cotreatment with an H_2-blocker or proton pump inhibitor usually indicates the presence of another cause of diarrhea or malabsorption; small intestinal bacterial overgrowth is the most common.

Management of Endocrine Insufficiency

Like exocrine insufficiency, endocrine insufficiency is typically a consequence of longstanding chronic pancreatitis. The relationship between diabetes and chronic pancreatitis is complex. Some patients with earlier stages of chronic pancreatitis have type 2 diabetes mellitus because of obesity and the metabolic syndrome. Some patients with long-term type 1 diabetes mellitus also develop chronic pancreatitis, but little is known about the mechanisms of this process. Patients with long-term chronic pancreatitis or extensive pancreatic resection can develop type 3 diabetes mellitus,[32] characterized by a lack of insulin and other counter-regulatory islet hormones, such as glucagon. These features cause more frequent treatment-induced hypoglycemia and low levels of glucagon, pancreatic polypeptide, and gastric inhibitory peptide and, on rare occasions, ketoacidosis.[32] Chronic pancreatitis is a risk factor for pancreatic cancer, and diabetes can increase this risk.[33] The use of an insulin-sensitizing agent such as metformin may reduce the risk of cancer in these patients. The exact prevalence of diabetes among patients with chronic pancreatitis is not known, but diabetes and

Table 2. Pancreatic Enzyme Products

Product	Formulation	Manufacturer	Lipase content (USP)/pill or capsule
Zenpep	Enteric-coated porcine	Aptalis	3000, 5000, 10,000, 15,000, 20,000
Creon	Enteric-coated porcine	Abbott	3000, 6000, 12,000, 24,000
Pancreaze	Enteric-coated porcine	Ortho-McNeil-Janssen	4200, 10,500, 16,800, 21,000
Pertzye	Enteric-coated porcine mixed with bicarbonate granules	Digestive Care	8000, 16,000
Ultresa	Enteric-coated porcine	Aptalis	13,800, 20,700, 23,000
Viokace	Tablet non–enteric-coated porcine	Aptalis	10,440, 20,880

impaired glucose tolerance are observed in many, depending on the stage of disease.

Diagnosis of diabetes in patients with pancreatitis relies on the same criteria as for all forms of diabetes: fasting plasma glucose level ≥126 mg/dL, 2-hour oral glucose tolerance test result >200 mg/dL, or hemoglobin A_{1c} ≥6.5%. Although there are no screening and surveillance guidelines for chronic pancreatitis, it is reasonable to perform tests for fasting plasma levels of glucose and hemoglobin A_{1c}, along with the standard glucose tolerance test, if findings are inconclusive. It is also reasonable to repeat these tests on a yearly basis.

Treatment of diabetes in patients with pancreatitis usually involves referral to an endocrine specialist. There are benefits to insulin therapy, but treatment-induced hypoglycemia is a potential disadvantage. Metformin may reduce the long-term risk of cancer but is often inadequate as a single agent to treat diabetes. Patients with low levels of insulin and C-peptide and low body mass would probably benefit most from insulin therapy but also have the highest risk of hypoglycemia.

Many additional complications can develop in patients with chronic pancreatitis, including osteoporosis, pancreatic pseudocyst formation, and pancreatic cancer. Although these are not discussed in detail, some aspects of management are outlined in Supplementary Table 3.

Conclusion

The management of patients with chronic pancreatitis has undergone significant changes over the past decade. Strategies to increase the accuracy of diagnosis, better assess symptoms and complications, and manage patients using multidisciplinary teams have improved the care of these patients. Consistent delivery of the best evidence-based care has the potential to improve the health of many patients with chronic pancreatitis. Unfortunately, we still have many patients who remain symptomatic despite our best efforts. Connecting these patients with support groups, such as the National Pancreas Foundation (www.pancreasfoundation.org), can increase the effects of treatment.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2013.02.008.

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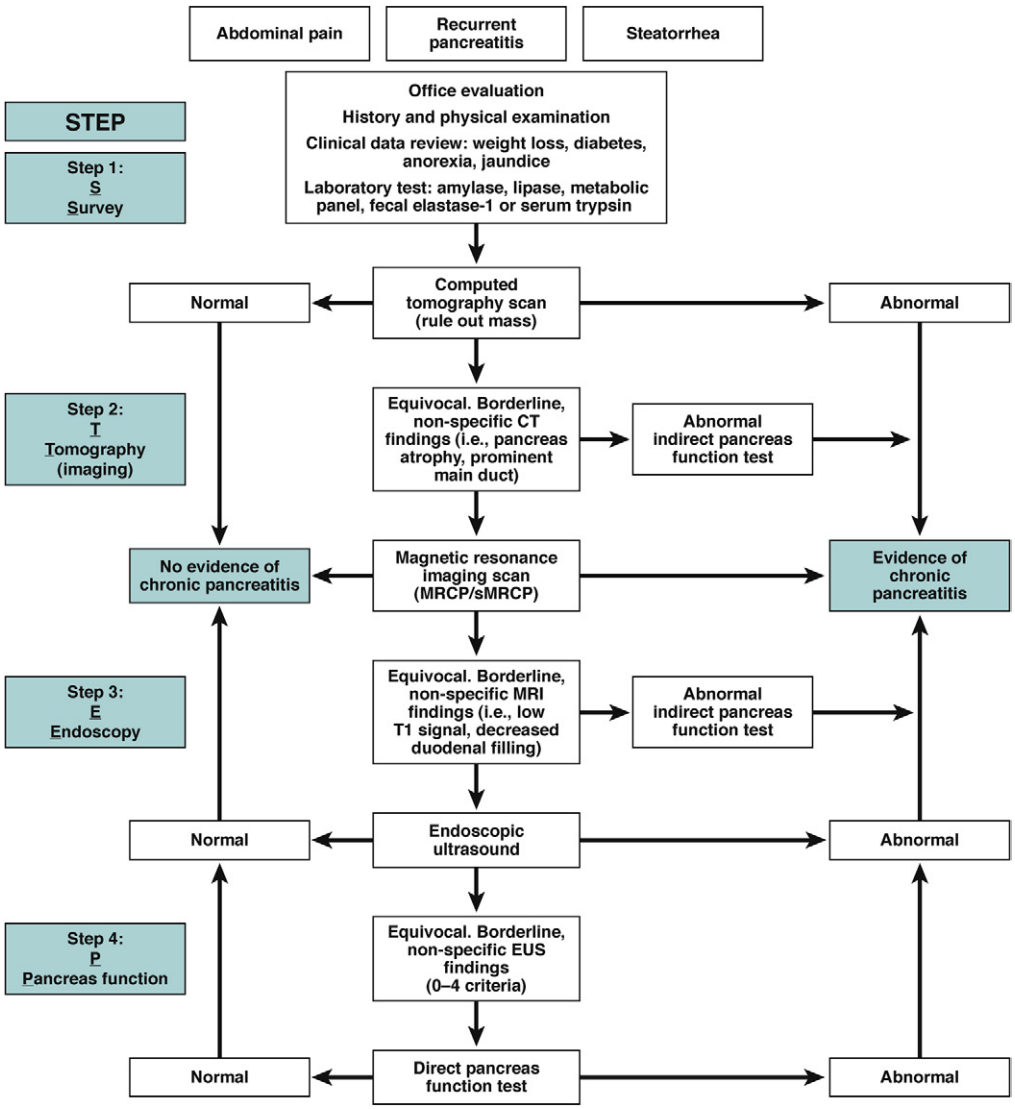
Conflicts of Interest

The author discloses no conflicts.



Supplemental Figure 1. A diagnostic algorithm for chronic pancreatitis.

Supplementary Table 1. TIGAR-O Classification System

Toxic metabolic
Alcoholic
Tobacco smoking
Hypercalcemia
Hyperlipidemia
Chronic renal failure
Idiopathic
Tropical
Cause unknown
Genetic
Autosomal dominant
Cationic trypsinogen
Autosomal-recessive/modifier genes
CFTR mutations
SPINK1 mutations
Chymotrypsin-C
Others
Autoimmune
Type 1
Type 2
Recurrent and severe acute pancreatitis
Postnecrotic (severe acute pancreatitis)
Vascular diseases/ischemia
Postradiation exposure
Obstructive
Pancreas divisum (controversial)
Sphincter of Oddi dysfunction (controversial)
Duct obstruction (tumors, posttraumatic)

Supplementary Table 2. Conditions Associated With Pancreatic Exocrine Insufficiency

Conditions	Presumed mechanism	Comments
Chronic pancreatitis	Acinar cell loss or injury	May be reversible (ie, corticosteroid treatment of autoimmune pancreatitis)
Severe acute (necrotizing) pancreatitis	Acinar cell loss	Transient exocrine insufficiency may develop after severe pancreatitis without necrosis
Shwachman–Diamond syndrome	Acinar cell dysfunction	Usual presentation in childhood with exocrine insufficiency, skeletal abnormalities, bone marrow dysfunction, and short stature
Pancreatic surgery	Acinar cell removal, often with asynchronous delivery of enzymes	
Intestinal surgery (eg, gastric bypass)	Asynchronous delivery of enzymes with meal	
Duct dysfunction	Cystic fibrosis	The majority of patients, but not all, are pancreatic insufficient
Duct blockage	Ductal adenocarcinoma, intraductal papillary mucinous neoplasm, stricture	
Zollinger–Ellison syndrome	Enzyme destruction	

NOTE. Courtesy of David C. Whitcomb, MD, PhD.

Supplementary Table 3. Complications of Chronic Pancreatitis

Complication	Usual clinical presentation	Management
Pseudocyst	May occur at any time Usual presentation is abdominal pain that is worse or different from chronic pain Need to differentiate from cystic neoplasms	Make sure the cystic collection does not represent a cystic neoplasm (history, EUS) Do not treat pseudocysts not causing symptoms, regardless of size Endoscopic and surgical drainage techniques are most commonly used, depending on anatomy and available expertise
Pancreatic cancer	The overall lifetime risk is up to 4%, but certain groups are at increased risk, including those who smoke, have coexistent diabetes, and have hereditary pancreatitis Worsening pain, weight loss, or obstructive jaundice	May be difficult to visualize a mass in the background of chronic pancreatitis; a combination of EUS and CT or MRI is most accurate
Duodenal obstruction	Most commonly occurs in those with an inflammatory mass in the head of the pancreas	Usually requires surgery with a DPPHR or Whipple operation
Biliary obstruction	Most commonly occurs in those with an inflammatory mass in the head of the pancreas	May respond to temporary endoscopic stenting, using multiple plastic stents of fully covered metal biliary stents May require surgery with a DPPHR, Whipple operation, or choledochojejunostomy
Osteopenia and osteoporosis	Seen in those with exocrine insufficiency, with similar risk as in patients with inflammatory bowel disease Risk increases with disease duration; may have associated deficiency of other fat-soluble vitamins	Baseline and periodic assessment of fat-soluble vitamin levels and bone density Routine supplementation with calcium and vitamin D is appropriate
Gastroparesis	A consequence of both chronic pancreatitis and narcotic analgesia	Can mimic some symptoms of chronic pancreatitis, including nausea and abdominal discomfort
Small intestinal bacterial overgrowth	Diarrhea, steatorrhea, bloating; mechanism not clear	Can mimic symptoms of exocrine insufficiency with malabsorption and diarrhea