Chapter 60

Management Strategies in Chronic Pancreatitis

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INTRODUCTION

Chronic pancreatitis (CP) is characterized by progressive and irreversible damage to the pancreas that eventually leads to pain and/or exocrine and endocrine insufficiency as well as malnutrition. In the majority of patients with CP, pain is the distressing as well as the most common symptom and indication for patient seeking medical help and intervention. Other indications for intervention include complications, such as pseudocysts, biliary or duodenal obstruction, internal or external pancreatic fistulae and left-sided portal hypertension, resulting from splenic vein thrombosis. The exocrine and endocrine complications can be managed medically.

The management strategies of CP involve correct diagnosis and staging of the disease as well as identification of the underlying etiology. Alcohol is the most common cause of chronic pancreatitis worldwide. Still in a large proportion of patients with CP no etiology can be identified and these are labeled as idiopathic chronic pancreatitis (ICP). However, with medical advancement various other factors like genetic mutations, hypertriglyceridemia, hyperparathyroidism and autoimmune have been found to be causative for CP. Subgroup of CP with no definite etiology has been labeled as ICP which includes a number of well-described disease entities like early and late onset ICP, tropical pancreatitis, minimal change CP and small duct CP.

In a study from Chandigarh clinical profile of 155 CP patients in north India revealed ICP was most common etiology seen in 41.8% followed by alcoholic CP in 38.1%, hyperparathyroidism as etiological factor seen in 3.2% of patients of CP. Mean age of presentation of patients was 36 ± 12.4 years and 78% were males and lower age of presentation in ICP as compared to alcohol related CP was noted. An another Indian study, collected data from 32 centers in India (1,086 patients) found an average age of only 39.7 years with 60% patients having ICP, 38% having alcoholic pancreatitis and classical tropical pancreatitis in 3.8%.

CLINICAL SIGNS AND SYMPTOMS

Abdominal pain is most common and morbid symptom occurring in majority of patients and is responsible for most hospital admissions related to CP. Indian studies have shown abdominal pain as presenting complaint in more than 90% patients. The pain is located in the epigastric area, often radiates to the back, dull or boring in quality and worsens after eating. There may be associated nausea and vomiting with exacerbations of pain which tends to last for hours unless relieved by injections. Initial belief that as the disease progresses spontaneous relief of pain may occur because disease gets burnout is being replaced by the fact that due to repeated episodes of inflammation, there occurs irreversible damage to pancreas which makes management of pain difficult. The disease can manifest with steatorrhea and weight loss and diabetes respectively. Pancreatic exocrine insufficiency may be mild, moderate or severe depending on stage of disease process, duration of disease and etiology but clinically apparent steatorrhea generally does not occur until 20–30% of pancreatic function has been lost. Endocrine insufficiency also occurs late in disease. It is reported to tune of 20–30% in various Indian studies. It can be controlled with diet, OHAs and insulin therapy. In our study, pain was the dominant symptom in patients with alcohol induced CP as well as ICP [91.5% and 96.8% patients respectively]. There was no significant difference in the body mass index (BMI) between patients with alcoholic CP as well as ICP (20.7 ± 3.6 Kg/m² vs 20.2 ± 3.5 Kg/m² respectively).

COMPLICATIONS

Various complications include pseudocysts, biliary or duodenal obstruction, internal or external pancreatic fistulae, left-sided portal hypertension and pancreatic malignancy. The typical clinical presentation of a pseudocyst is worsening abdominal pain in the setting of known CP, with or without mild elevation in the serum amylase and lipase levels. Although they may be asymptomatic but usually in setting of CP spontaneous resolution is less because of altered ductal anatomy. Pseudocyst itself may cause symptoms like pain abdomen, gastric outlet obstruction, and biliary obstruction or gets complicated by infection, hemorrhage or rupture etc. Pancreatic ascites and pleural effusions arise from a communication of pancreatic pseudocysts with adjacent cavities or from disruption of the pancreatic ducts (PDs). Duct disruption anteriorly results in pancreatic ascites and dorsal disruptions leads to pleural effusion which can occur on either side but left pleural cavity is more often involved. These are exudative (low SAAG) in nature and are diagnosed on the basis of elevated fluid amylase content. The splenic vein thrombosis is common and portal hypertension resulting is called left sided portal hypertension. It is usually asymptomatic but recurrent bleeding from gastric varices develops in some patients. Occasionally, bleeding may occur from an arterial pseudoaneurysm.

HOW TO DIAGNOSE CHRONIC PANCREATITIS?

Diagnosis is based on the history of chronic pain and demonstration of morphological and/or functional changes that typically develop overtime in the course of the disease. The morphological changes may be in the form of parenchymal changes in gland like atrophy/ enlargement of gland, calcifications, and ductal changes like dilated main pancreatic duct (MPD) with dilated side branches or stricture,
disruption or calcui in the MPD or presence of pseudocyst. Imaging modalities are needed to demonstrate these changes.

Plain abdominal X-rays and ultrasound (USG) abdomen can be used as a screening test as they are inexpensive, noninvasive and specific, but they are less sensitive. The finding of pancreatic calcifications on abdominal plain film is almost 100% specific but poorly sensitive (30-70%) for the diagnosis of CP. In patients with thin bodies, transabdominal USG may detect parenchymal and ductal features suggestive of CP (sensitivity, 60-70%; specificity, 80-90%). USG also helps in ruling out other causes of abdominal pain, such as gallstones.

Contrast enhance CT with pancreatic protocol is reliable in picking up changes of CP in the form of atrophy, duct dilatation and calcifications. Using these criteria, CT has a sensitivity rate for advanced CP of 74-90% and a specificity of 84-100%. Additionally, CT allows the detection of complications of CP; including pseudocysts, splenic artery pseudoaneurysm, biliary obstruction, pancreatic ascites and effusion, splenic and portal venous thrombosis and inflammatory mass in the head of pancreas. The finding of pancreatic head enlargement may warn a pancreatic cancer or an inflammatory mass. However, diagnosis of CP in early stage is still a challenge. Endoscopic ultrasound (EUS), magnetic resonance cholangiopancreatography (MRCP), and secretin-enhanced MRCP are imaging modalities that have enhanced sensitivity for diagnosing early CP. EUS has added advantage for closely seeing parenchyma, better characterization of pseudocyst wall, contents, vascular structure in vicinity, allows diagnostic aspirations in case of suspicion of malignancy and provides road map for endoscopic drainage procedures. Early stage CP may be better diagnosed by direct pancreatic function tests but they are invasive and cumbersome.

**TREATMENT OF CHRONIC PANCREATITIS AND ITS COMPLICATIONS**

Morphological changes in pancreas occur over period of time and depending upon that, it can be classified as early or definite CP, calcific versus noncalcific CP and small or large duct CP. CP can be classified as small duct disease (< 5 mm) and big duct disease (> 5 mm) depending on duct diameter on imaging and it has important management implications. After establishing a correct diagnosis based on history, examination and imaging computerized tomography/MRI and MRCP (if possible secretin MRCP and EUS), we should look for PD dilatation, strictures, or ductal calculi and also look for functional insufficiency which can be exocrine and/or endocrine.

The essential aspects of managing a patient with CP involve: (1) amelioration of pain; (2) maintain nutrition and control maldigestion; and (3) Tackle complications.

**CONTROL OF ABDOMINAL PAIN**

The goal of therapy is to control pain to that level that it may not hamper patient’s life as complete relief of pain is not expected.

**Medical Therapy**

This can be used in all patients; combination of drugs can be used. Abstinence from alcohol and smoking is strongly recommended.

**Analgesics**

A step-up approach is usually used for pain relief. Initially, non-narcotic analgesics [e.g. nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen] are used and if there is insufficient relief, a combination therapy of peripherally acting medication with centrally acting medication like combining a nonopioid analgesic with a weak opioid such as tramadol can be used. Tricyclic antidepressants (TCAs), SSRIs, combined serotonin and norepinephrine reuptake inhibitor may be used in patients with associated depression. In selected cases with severe or recalcitrant pain stronger opiates can be used. Pregablin, a GABA agonist, has also been shown to be effective.

**Pancreatic Enzymes**

Pancreatic enzymes are proposed to improve pain by suppressing CCK release from the duodenum; one of mechanism of pain is increased CCK level and hyperstimulation in CP. However, results of various trials using pancreatic proteases for pain are discordant. The reasons could be variable natural history of pain, multiple factors for its causation, placebo response rates up to 35% as well as use of enteric-coated versus nonenteric-coated preparation. Young women with ICP have shown best response, whereas patients with advanced disease, including those with steatorrhea, did not have any response. Of the six randomized trials published to date two studies using a nonenteric-coated enzyme preparation reported benefit and four studies using an enteric-coated capsule showed no effect on pain in CP. A meta-analysis of the six randomized, double-blind, placebo-controlled trials for the treatment of CP with pancreatic enzymes showed no benefit in improving pain. It should be noted that this meta-analysis combined studies using enteric-coated and studies using nonenteric-coated preparations. Uncoated preparation works well by enhancing delivery to the proximal small bowel. Uncoated pancreatic enzymes trial should be given to patients for 6-8 weeks and if effective it should be continued.

**Antioxidants**

Oxidative stress has been proposed to play a role in the pathogenesis of pancreatic injury. Several small observational studies suggested benefit. A recent randomized, placebo-controlled trial by Bhardwaj et al. on antioxidants [mixture of selenium (600 µg), methionine (2 gm), vitamins E (270 IU) and C (540 mg), and β-carotene (9,000 IU)] demonstrated significant pain relief with antioxidants in patients of chronic pancreatitis. In this study majority of patients had ICP. But another randomized placebo controlled trial from UK with majority of patients being alcoholic CP did not show any significant reduction in pain.

**Pregabalin**

Increase glutamate which in turn increases GABA. Initial dose: 75 mg twice daily 3 days, later: 150 mg twice daily 1 week, later: 300 mg twice daily (till next 3 weeks) caused significant relief in pain. Side effects like feeling drunk and light-headedness can be seen.

**Nerve Blocks**

Nerve blocks are being described below.

**Miscellaneous Therapies**

Following therapies have been tried: Interferon α and β, Saiko-keishi-to (TJ-10), curcumin, PPAR-gamma ligand (troglitazone), statins, oral protease inhibitor: camostat, calcitonin gene related peptide antagonists, neurokinin-1 receptor antagonists, LT antagonist: zafirlukast, CCK-receptor antagonist: loxiglumide and spinal cord stimulation.

If the patient responds to medical therapy then the same may be continued but if there is no response to a trial of medical therapy and patient has large duct disease, then patient needs to be evaluated for possible endoscopic or surgical therapy.
Interventional Treatment

Obstruction of the MPD from stones and strictures leads on to increased ductal and parenchymal pressure, resulting in pain. In this scenario, decompression of the PD by either endoscopic or surgical drainage procedures can be effective. Endoscopic approaches are challenging and available at specialized centers. Before initiating endoscopic therapy for abdominal pain, other causes like pseudocyst, bile duct stenosis, gastric outlet obstruction and pancreatic malignancy should be excluded.

The disease needs to be first characterized into large or small duct CP depending upon the diameter of the MPD. Large duct disease can be treated with endoscopic or surgical decompression with good results but in patients with small duct disease options are limited to medical management with analgesics, enzymes, antioxidants, nerve blocks and surgery.

The aim of the endotherapy is to relieve pain by alleviating outflow obstruction of PD and decrease ductal hypertension. In this case of PD strictures can be achieved by dilating the stricture and placing stent/s and in patients with PD stones this can be achieved by removing or breaking the stones. Pancreatic sphincterotomy, i.e. cutting the pancreatic sphincter so as to increase the diameter of the working outlet is mandatory for stone extraction and may be done for progressive stricture dilatation. Pancreatic endotherapy is usually successful in patients with single stricture/stone located in head or proximal body. Single stone less than 1 cm size in head with no proximal stricture can be removed endoscopically. The stones can be removed by various endoscopic techniques like balloon sweep, lithotripsy (mechanical, extracorporeal shock wave lithotripsy followed by balloon sweep, or electrohydraulic shock wave lithotripsy), or stone retrieval using a basket. A case series of more than 1,000 patients from eight high volume centers in Europe, with 12 years of follow-up had shown endotherapy controlled pain in 75% of patients and 25% patients required surgery. In retrospective analysis by us, ESWL was used in 87 patients with MPD stone (5–15 mm in size and multiple in 53 patients) that could not be extracted with usual endoscopic method. Patients were subjected to ESWL followed by endoscopic duct clearance. 54% patients had complete or partial MPD clearance and only 10% had elective surgery over follow-up of 24–92 months. Endotherapy has success rate for more than 90% in CP series reported from Chandigarh with only 9% patients requiring surgery for pain relief.

Surgical therapy is usually reserved for patients with pain not responding to both medical and endoscopic therapy or in whom endoscopic therapy is difficult like multiple and distal strictures, large, multiple and impacted stone. Surgery is performed in view of “need for long-term narcotic therapy, marked diminution of the quality of life because of intractable pain, or major nutritional consequences of pain.” The surgical techniques to relieve pain include resection, decompression, or combination of both. The modified Puestow or lateral pancreaticojejunostomy is the most commonly performed decompressive surgery. More complex surgeries include restorative surgeries like traditional pancreaticoduodenectomy (Whipple operation), a limited resection of the pancreatic head (Beger operation), or combination of both resection as well as drainage like combined opening of the PD and evacuation of some of the pancreatic head (Frey operation).

Although both endoscopic as well as surgical therapy are effective, a recent randomized study has shown that surgery is better than endoscopic therapy for both short as well as long-term relief of pain. However, majority of the patients included in the endoscopic group in this study had distal tail end strictures and patients were offered short-term stenting. Therefore, the final word is still not out and because of being minimally invasive, endotherapy may be offered first. Patients with multiple ductal strictures, strictures in tail of pancreas, multiple/large pancreatic ductal calculi and patients with inflammatory mass may be preferentially offered surgery.

Nerve Blocks

A subgroup of patients with CP has refractory abdominal pain and in these patients, nerve blocks have been explored. Celiac plexus blockade (CPB) and celiac plexus neurolysis (CPN) are the nerve block methods used to disrupt the signaling of the pancreatic pain afferents to the spinal cord. CPN is permanent ablation of celiac plexus usually done for pancreatic malignancies that is achieved by injection alcohol or phenol administered with local anesthetic such as bupivacaine whereas CPB is temporary inhibition of celiac plexus caused by injection of corticosteroid in combination with bupivacaine. These blocks can be achieved radiologically using computed tomography (CT) or surgically. Recently, EUS has been used to achieve blocks and studies have shown that it is superior in terms of efficacy as well as safety to radiological techniques. Although these procedures have good initial response but long term results are not encouraging.

CHRONIC PANCREATITIS AND PANCREAS DIVISUM

Pancreas divisum (PD) is the most common congenital variant of pancreatic ductal anatomy and in this anatomical variation pancreatic juice is drained predominantly through the accessory or minor papilla. Majority of patients with PD are asymptomatic but a subset of patients may present with recurrent acute pancreatitis, CP, or chronic abdominal pain. It has been proposed that in patients with PD when the minor papilla is critically small, a relative outflow obstruction to the pancreatic juice leads to high intraductal pressure and consequent pain. In these patients, by opening up the minor papilla sphincter endoscopically or surgically the pain may be relieved. Endoscopic therapy involves minor papillotomy or dorsal duct stenting or both. There are a number of studies that have evaluated the efficacy of endoscopic therapy for PD and most of these studies have shown that best results are obtained in patients with acute recurrent pancreatitis and results of endoscopic therapy in patients with PD and CP are not good. However, in a large series of 48 patients, we have shown that pancreatic endotherapy is safe and effective both in patients with chronic calcific as well as non-calcific pancreatitis associated with PD and gives good long-term response in patients having abdominal pain and/or dorsal ductal disruptions.

MANAGEMENT OF COMPLICATIONS OF CHRONIC PANCREATITIS

Pseudocyst

Mere presence of pseudocyst on imaging studies is not an indication for intervention. Earlier, a size cut-off of approximately 6 cm was used as a criterion for drainage of a pseudocyst. However, studies have shown that patients may remain asymptomatic with pseudocysts of more than 6 cm with little risk of complications and any intervention is associated with complications. Therefore, patients with asymptomatic pseudocysts are usually followed-up and intervention is to be done only in symptomatic patients. The symptoms related to pancreatic fluid collections (PFCs) include abdominal pain, weight loss, gastric outlet obstruction, obstructive jaundice, and PD leakage leading on to ascites or effusion. Presence of infection in the pseudocyst is an absolute indication for drainage.

The drainage can be achieved by percutaneous, endoscopic (with or without endoscopic ultrasound guidance) or surgical procedures.
Radiological drainage should be done only in patient poor risk for endoscopic or surgical procedure in emergency indications because external drainage leads to external pancreatic fistula, increases secondary infection rate and outcome of later surgery in negatively affected. Endoscopic procedures are favored over surgery because of good success rate and being less invasive. Before planning intervention, diagnosis and location of pseudocyst must be confirmed. Malignancy and hemorrhage in pseudocyst must be ruled out and pancreatic ductal anatomy should be outlined on MRCP to look for associated stricture, stone, disruption in MPD or its communication with cyst. Endoscopic drainage can be done through transmural or transpapillary approaches or combined. The transmural drainage involves the drainage of the pseudocyst in to the gastrointestinal tract by puncturing it through the stomach or duodenum. EUS guidance can decrease the complications of the transmural procedures by allowing the procedure under vision and thus avoiding vascular collaterals. The transpapillary drainage involves cannulation of the PD through the major or minor papilla and thereafter documentation of PD disruption by injecting contrast. PD disruption is defined as complete when the main duct upstream to the disruption is not opacified and as partial when the main duct is visualized upstream from the site of disruption. After confirming the ductal disruption, stent or nasopancreatic drain (NPD) is placed across the papilla in to the PD by advancing it over a hydrophilic guide wire. An attempt should be made to place the endoprosthesis across the area of the disruption for the best results. The decision to use one approach over the other depends on the size of the pseudocyst, its proximity to the stomach or duodenum, and the ability to enter the PD and/or reach the area of disruption. The transpapillary drainage is effective if the pseudocyst communicates with the MPD, and is less than 6 cm in size. Transpapillary drainage is usually avoided in larger pseudocysts because of risk of infection although we have shown that transpapillary drainage with a NPD is safe and effective in patients with multiple and large pseudocysts. Advent of EUS has revolutionized endoscopic treatment and risk of complications has decreased as collaterals can be easily seen and carefully avoided while puncturing the pseudocysts and importantly non bulging pseudocysts can be easily treated.

**Pancreatic Ascites and Pleural Effusion**

Bowel rest, parenteral nutrition and subcutaneous octreotide are part of medical management but with excellent results of pancreatic endotherapy, the medical therapy is now rarely used. Endoscopic transpapillary nasopancreatic or stent drainage has been shown to be effective in treating pancreatic ascites and pleural effusion. Those with downstream stricture or stone or complete disruption are difficult patients and may need surgery after either failed or no response to endoscopic therapy.

**Other Complications**

Vascular complications may occur in form of segmental portal hypertension with gastric varices which bleed rarely and may be tackled with glue injection. Arterial pseudoaneurysm may occur most commonly in relation to splenic artery. Various therapeutic options available are percutaneous USG or EUS guided thrombin injection, coil embolization or surgery. Biliary and duodenal obstruction can also be treated endoscopically but surgery has better long lasting results and therefore, is preferred. Newer removable self-expanding metal stents are being evaluated in these patients and long-term results are being eagerly awaited. Last but not least, CP patients have risk of pancreatic malignancy. No screening protocol is recommended but warning signs of rapid weight loss with increasing pain and anorexia should be investigated.

**ENDOCRINE AND EXOCRINE INSUFFICIENCY**

**Maldigestion**

The maldigestion in CP is treated by oral enzyme supplementation. But we should remember that none of the commercially available enzyme preparations is able to deliver more than 360,000 IU of active lipase into the duodenal lumen, that are secreted by the normal pancreas. Does that mean that oral enzyme supplementation would not be able to treat maldigestion? Inspite of this limitation, enzyme therapy is effective in majority of the patients because of the effect of gastric lipase and residual pancreatic lipase. The enzymes are most effective if they are enteric-coated preparations in the form of minmicrospheres and gastric emptying of the enzymes occurs in parallel with nutrients. To achieve this, enzyme preparation should be administered together with meals. A minimum of 30,000 IU lipase with each meal allows adequate intraluminal digestion of fat and protein. The dose needs to be titrated to as much as 60,000–80,000 IU lipase per meal and with snacks 10,000–25,000 IU can be supplemented. The response to enzyme therapy can be monitored through an assessment of steatorrhea related symptoms, weight gain, 72-hour stool fat quantification, normalization of mixed 13C-triglyceride (13C-MTG) breath test. A poor response to pancreatic enzymes may suggest noncompliance, loss of enzyme potency, improper timing of enzymes in relation to meals, or coexisting mucosal disease. A trial with proton pump inhibitors to inhibit gastric acid may be attempted and in some patients this may improve steatorrhea.

**Endocrine Insufficiency**

Pancreatic endocrine insufficiency secondary to CP ranges in severity from mild form that is easily controlled with oral hypoglycemic agents to severe form requiring increasing doses of insulin for proper glycemic control. The diabetes in this setting is particularly difficult to manage because of brittle fluctuations of hyperglycemia and hypoglycemia, especially in patients who have undergone surgery like total or subtotal pancreatectomy.

**CONCLUSION**

Inspite of the progress made in our understanding of the pathogenesis as well as the treatment of CP over last several decades, it still remains an enigmatic disease with majority of the treatment strategies hovering around palliation of its consequences rather than treating and reversing the pancreatic damage. The pain is the predominant consequence of CP and in majority of the patients it can be effectively controlled by medical or endoscopic therapy with few patients requiring surgery. The endocrine and exocrine insufficiency can be safely and effectively treated with medical therapy and maintaining the nutritional status should be an important goal of the medical therapy. And also, as these patients have increased risk of pancreatic malignancy, patients with warning signs like rapid weight loss with increasing pain and anorexia should be investigated for pancreatic cancer (Flow chart 1).
Flow chart 1: Management algorithm for chronic pancreatitis

1. Endocrine insufficiency
   - Diet, insulin, Oral hypoglycemic agents

2. Pain
   - Exclude complications like pseudocyst, biliary or duodenal obstruction, malignancy
   - Trial of medical therapy including analgesics, antioxidants and pancreatic enzymes
   - Small duct disease
     - Analgesics
     - Enzymes
     - Antioxidants
     - Pregabalin
     - Nerve block
     - Surgery

3. Exocrine insufficiency
   - Enzyme supplementation

4. Chronic pancreatitis

5. Large duct disease
   - Endoscopic Pancreatic endotherapy:
     - Stricture dilatation
     - Stent insertion
     - Stones removal
     - Minor papillotomy
   - Pancreatic head mass
     - Multiple strictures
     - Strictures at tail end of pancreas
     - Multiple large ductal calculi
     - Duodenal obstruction

6. Pain persists

7. Fails

8. Surgery

BIBLIOGRAPHY