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Follow-up of Patients with Chronic Pancreatitis in Clinical Practice

How and What for?

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Introduction

Chronic pancreatitis (CP) is characterized by irreversible fibrosis of the pancreatic parenchyma that leads to a syndrome characterized by persistent pain and the metabolic derangements that arise from loss of the exocrine and endocrine functions of the gland. Calcifications, pancreatic duct stones and/or strictures occur later in the course of the disease but are not invariably present. The prevalence of CP is estimated to be 13.5–52.4 per 10 000 population, but the data from historical postmortem series indicate that the condition is significantly underreported. This is secondary, in part, to the challenges in establishing an accurate diagnosis, especially during the early stages of the disease. In this chapter we provide a guide to the diagnosis and routine management of patients with CP for the clinician treating patients with this condition.

Pain

Pain is the cardinal symptom of CP, and yet the most difficult to assess and treat. This is mostly due to its heterogeneity as an entity as well as to its inherent subjective perception by the patient experiencing it. The current concept of pain in CP is that of a multifactorial epiphenomenon in which intraductal/intraparenchymal pressures represent just part of the spectrum (Figure 34.1).

Currently accepted pathways resulting in pain in CP include the following.

Mechanical Obstruction

Interference with the normal drainage of the organ results in nociceptive stimuli due to ductal dilatation. This theory is supported by the fact that relieving obstructions (stones and/or strictures) in the drainage system can improve pain [1,2].

Neurogenic

- *Peripheral nociception*: parenchymal changes lead to increased concentrations of proinflammatory cytokines, rendering the peripheral nociceptors prone to stimulation and spontaneous/continuous activity [3–5].
- *Pancreatic neuropathy*: anatomical changes in the intrapancreatic neurons (hypertrophy, increased neural density and sprouting) are associated with pain scores [6–8].
- *Central pathways*: constant nociceptive stimuli from peripheral nerves results in an abnormal, persistent, and exaggerated perception of pain [9–11].

Assessment of pain in patients with CP can be a daunting task. Different scales are available, all with their own advantages and disadvantages. One-dimensional numeric scales provide simple and fast assessments of pain intensity. The pitfall of these scales is that they oversimplify the pain experience [12]. Therefore it is recommended that they are used in conjunction with a register of the pain pattern (intermittent vs. constant) [13].

Multidimensional scales measure several aspects of pain (intensity, nature, impact on mood or activity level). The benefit of these scores is that they provide insight into the impact of pain on the patient's quality of life [14,15]. A recent publication outlines our current understanding and management of pain in CP [16]. As such, the management of pain in CP should encompass a broad and ideally multidisciplinary approach. Several options are available for its management, and ideally treatment should include agents that target more than one of the accepted pathways.

Pancreatic Enzyme Replacement Therapy

The basis of using pancreatic enzyme replacement therapy (PERT) for pain is the notion that nutrients stimulate the release of cholecystokinin-releasing factor (CRF) [17].

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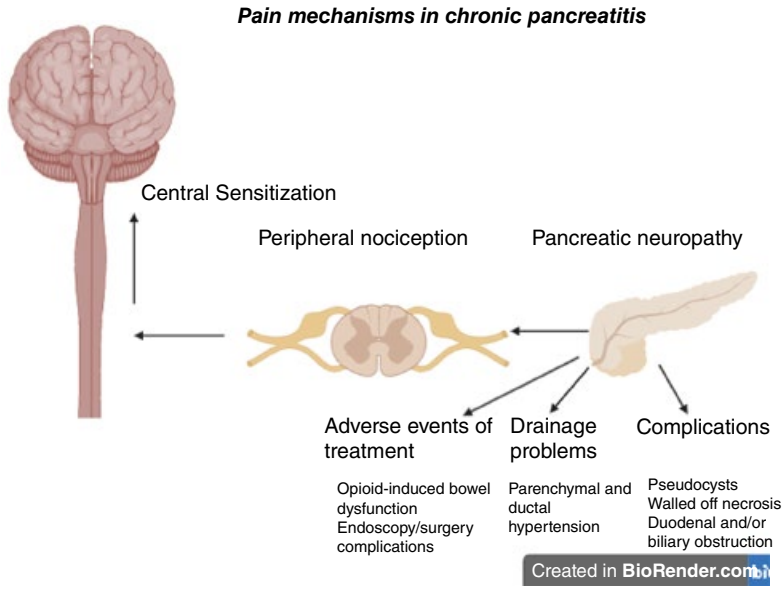

Figure 34.1 Pain mechanisms in chronic pancreatitis. *Source:* courtesy of Antonio Mendoza-Ladd, Luis F. Lara, and Darwin L. Conwell

Cholecystokinin (CCK) in turn stimulates pancreatic secretion, leading to a rise in intraductal pressures. The effect of PERT on CP pain has been studied in several trials with conflicting results [18–23]. Interestingly, those trials in which PERT was not effective used enteric-coated formulations only [20–23]. Therefore if PERT is used for pain relief, only uncoated enzyme preparations should be used [16], although this indication remains controversial [24].

Antioxidants

Oxidative stress has been linked to pain in CP [25]. Antioxidants such as vitamins A, C and E, selenium, and methionine have shown significant pain relief when used in combination in some studies and meta-analyses. However, single antioxidant therapy has not shown benefit, and it is not clear if this therapy is effective only in certain subtypes of CP [26–28].

Analgesics

The use of analgesics should follow a stepwise escalation of drugs, with increasing analgesic power (Figure 34.2). Simple analgesics such as acetaminophen and/or nonsteroidal anti-inflammatory drugs (NSAIDs) can be used as a first step. Caution should be exercised with NSAIDS as they can cause side effects that may worsen symptoms (i.e. peptic ulcer disease). The second acceptable step can be adding adjuvant therapies. These include antidepressants, anxiolytics and/or anticonvulsants. These drugs exert beneficial effects in patients with chronic pain, although no study has shown their benefit. Pregabalin has shown a modest beneficial effect in CP pain [29]. If schedule II drugs are necessary, tramadol is a preferred drug [30]. Opioids should only be used if no relief is obtained with any of the above-mentioned therapies. Importantly, opioids may cause side effects that may worsen pain (constipation, narcotic bowel syndrome) and only about 25% of patients experience benefit from them. Patients on opioids should be maintained under strict clinical surveillance due to their addictive properties [16].

Endoscopic Therapy

The basis of endoscopic therapy (ET) in CP consists of stent placement and/or stone extraction. Patients who benefit the most from ET are those with obstructing stricture/stone in the distal main pancreatic duct (head), especially with associated ductal dilation, and those in the early stage of the disease (two to three years from diagnosis). Extracorporeal shock-wave lithotripsy with or without ET has shown excellent results (91% stone clearance and up to 50% in pain control) [31–33]. Benefit from ET tends to be short-lived.

Surgery

Surgical treatment seems superior to ET and provides more long-term benefits based on a limited number of trials [34–36]. In two of these trials ET was compared to surgical intervention. The surgical group had better results at two to five years. In a third trial, surgical versus conservative management were compared; and the results favored surgery. These studies have suffered major criticism regarding patient selection, type of CP, and ET used. Despite the criticism, surgery has shown beneficial results and should be considered in patients early in the course of the disease

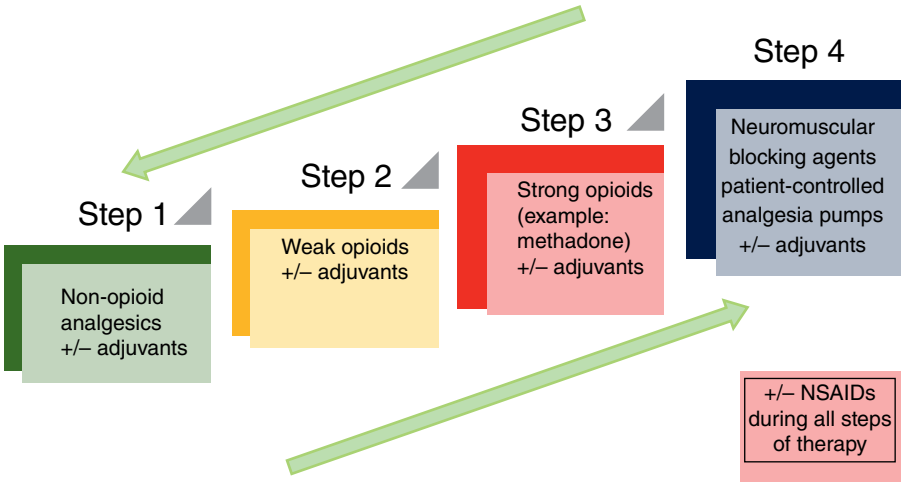

Figure 34.2 Analgesic ladder in chronic pancreatitis. *Source:* adapted from Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. *Can Fam Physician* 2010;56(6): 514–517.

(about two years) [37]. Notably, prior opioid use and five or more endoscopic interventions seem to have a negative influence on outcomes [38,39].

Other pain management options with highly variable results include celiac plexus block, thoracoscopic splanchnic denervation, spinal cord stimulation, and transcranial magnetic stimulation. Noninvasive options include behavioral therapy and hypnosis.

Nutritional Deficiencies

Malnutrition is a common phenomenon in CP, especially among those with exocrine pancreatic insufficiency (EPI). Malnutrition ensues due to a combination of factors, such as pain worsened by meals resulting in decreased oral intake, persistent vomiting, and malabsorption. Clinical signs of specific nutrient malabsorption subsequently develop (Table 34.1).

Establishing the diagnosis of malnutrition is important. Patients with CP can be screened with the community Malnutrition Universal Screening Tool (MUST) or hospital Nutritional Risk Screening (NRS-2002) [40]. The following physical examination measurements should be assessed: mid-arm circumference, triceps skinfold, and hand-grip strength. Laboratory investigations can include albumin, retinol-binding protein, prealbumin/transthyretin, fat-soluble vitamins (A, D, E and K), zinc, and magnesium [41–46].

Nutritional therapy in patients with CP is best achieved with the support of a dietitian. In general, fat-restricted diets as well as those with high fiber should be avoided. Patients with vitamin D deficiency should be treated accordingly, either orally or via the parenteral route. Recommendations regarding supplementation of other lipid-soluble vitamins are unavailable.

The development of sarcopenia, osteopenia, and osteoporosis should receive special emphasis [47,48]. Sarcopenia has been recently associated with increased mortality [47]. It is plausible to hypothesize that sarcopenia may be the inciting factor that leads to a decrease in weight-bearing exercise, which in turn results in osteopenia and osteoporosis. The latter are further worsened by malabsorption of vitamin D and calcium [48]. All patients should be counseled on adequate calcium and vitamin D intake, regular weight-bearing exercise, and smoking/alcohol avoidance. While there are no specific guidelines for bone health in CP, it is recommended that dual-energy X-ray absorptiometry (DEXA) scans be performed every two years in osteopenic patients. Those with osteoporosis should be referred for treatment and evaluation of other causes [49].

Most patients do not require oral nutritional supplements. Exceptions are those who cannot meet their nutritional requirements orally despite dietary intervention. When enteral nutrition is required, the nasojejunal route is recommended [24]. Jejunostomy feeding tube should be considered

Table 34.1 Consequences of exocrine pancreatic insufficiency.

Deficiency	Outcome
Vitamin A	Night blindness
Vitamin D	Osteomalacia, hypocalcemia
Vitamin E	Neuropathy, hemolytic anemia
Vitamin K	Coagulopathy
Fat malabsorption	Weight loss
Hypoproteinemia	Edema
Carbohydrate malabsorption	Bloating, diarrhea

Source: data from Pezzilli R. Chronic pancreatitis: maldigestion, intestinal ecology and intestinal inflammation. *World J Gastroenterol* 2009;15(14):1673–1676.

in those requiring enteral nutrition for longer than 30 days. Enteral nutrition should be combined with PERT.

Diabetes

Pancreatogenic or type 3c diabetes is also a manifestation of CP, although its incidence is variable [50]. In type 3c diabetes, insulin resistance and beta-cell dysfunction contribute in different degrees and stages [51]. Risk factors include surgical intervention (especially distal pancreatectomy), increasing age, smoking, presence of calcifications, and duration of disease [49].

Current recommendations for diagnosing pancreatogenic diabetes include fasting plasma glucose of 126 mg/dl (7.0 mmol/l) or greater, and HbA_{1c} of 6.5% (48 mmol/mol) or greater [52]. HbA_{1c} below 6.5% does not rule it out due to the limitations of this test. Therefore, normal HbA_{1c} (<6.5%) should always be confirmed by fasting plasma glucose. If the diagnosis is still equivocal, repeat testing or a standard 75-g oral glucose tolerance test is indicated. Testing for pancreatogenic diabetes should be performed annually.

Pancreatogenic diabetes is usually characterized by the absence of type 1 diabetes mellitus-associated autoantibodies plus at least two of the following four criteria: impaired beta-cell function as evaluated by homeostasis model assessment (HOMA)-B or C-peptide/glucose ratio, absence of excessive insulin resistance, impaired incretin (GIP or GLP-1) secretion, and deficiency of fat-soluble vitamins and/or micronutrients [50].

In the rare cases where the diagnosis remains equivocal, a pancreatic polypeptide (PP) deficiency test can be performed. Pancreatogenic diabetes develops in the setting of both insulin and PP deficiency [53]. A less than twofold increase from baseline levels of PP in response to a mixed-nutrient meal can help in establishing the diagnosis [54].

The goals of treatment are extrapolated from the recommendations for type 1 and 2 diabetes mellitus. Treating pancreatogenic diabetes may require a nutritionist and an endocrinologist [55]. Appropriate PERT is essential. Weight loss, exercise, low-carbohydrate diet, and abstinence from alcohol and/or smoking should be encouraged. In cases of severe malnutrition, insulin is commonly used as a first choice due to its desired anabolic effects [24]. If insulin resistance is present, metformin may be used. Sulfonylureas, glinides, thiazolidines, α-glucosidase inhibitors, incretin-based therapies, and sodium glucose cotransporter (SGLT)-2 should not be used due to risk of hypoglycemia and prominent side effects, including acute pancreatitis [24,56–59].

It was previously accepted that pancreatogenic diabetes was not associated with macrovascular complications. However, recent studies have challenged that assumption, with reports that cardiovascular events are the most common cause of death in these patients [60,61].

Exocrine Insufficiency

Approximately 60–90% of patients with CP will develop EPI within 10–12 years from the diagnosis [62]. While overt maldigestion is relatively simple to diagnose, EPI is also associated with more subtle and often elusive specific nutrient deficiencies, such as zinc, magnesium, prealbumin, and retinol-binding protein. Clinicians should be prompt in diagnosing and treating EPI because it not only impacts the patient's quality of life [63], but has recently been linked to an increased risk of mortality [64]. The diagnosis of EPI can be assessed through tests of pancreatic function. These are usually divided into direct and indirect tests.

Functional Tests

Direct Tests

These are the most sensitive tests available. Their drawbacks are their invasiveness, complexity, and limited availability. The classic example is the collection of pancreatic secretions via a double-lumen (Dreiling) tube. Once the device is in place intravenous secretin is administered, typically as a bolus dose of 0.2 μg/kg. Duodenal aspirates are obtained at baseline and then at 15-minute intervals for a total of 60 minutes. A bicarbonate concentration below 80 mmol/l in all four samples is diagnostic for EPI [65]. An endoscopic version of this test is also available [66]. Secretin can be substituted with CCK with comparable results [67].

Indirect tests

Despite variable sensitivity and specificity, these are the most widely used due to their simplicity, low cost, and wide availability.

Fecal Elastase Quantification of fecal elastase is the most commonly employed indirect test. There are five isoforms of this enzyme (CELA1, CELA2A, CELA2B, CELA3A, and CELA3B). Available commercial assays quantify CELA2 and/or CELA3 isoforms of the human "chymotrypsin-like elastase" via ELISA with polyclonal antibodies [68]. However, a more specific monoclonal fecal elastase-1 test is the most appropriate for clinical practice since it is not affected by PERT [69,70]. Elastase-1 is a proteolytic enzyme produced by pancreatic acinar cells. It binds to bile salts and passes through the gut with negligible degradation, making it quantifiable in feces. The concentration of this enzyme in feces reflects the level of pancreatic output and also correlates with the output of other pancreatic enzymes such as lipase, amylase, and trypsin [71,72].

A concentration below 200 μg/g is considered abnormal. However, there is no consensus regarding the cutoff for EPI in patients with CP: figures of less than 15, 50, 100 and 200 μg/g have been proposed [73,74]. The cutoff value of 200 μg/g has been adopted following the notion that levels below this are clearly suboptimal. Using this cutoff, the test has a specificity of 93% in patients with EPI but its sensitivity for mild EPI has been reported to be 63% [75]. Therefore, guidelines agree that it cannot exclude mild to moderate EPI [76]. The measurement must be performed on solid stool, since liquid stool can yield a false-positive result.

Fecal Chymotrypsin Chymotrypsin is another quantifiable pancreatic enzyme, but is variably degraded in the gut. The specificity of fecal chymotrypsin for EPI is lower than that of fecal elastase-1 [77,78]. It can be used to establish compliance with PERT.

Breath Tests These tests consist of oral administration of a ^{13}C-marked test meal. The substrates are hydrolyzed and the ^{13}C released and exhaled through the lungs in proportion to the amount of pancreatic lipase activity. Breath samples are collected in collection tubes, and the exhaled $^{13}CO_2$ is quantified. The advantage of this test is that it can be modified by PERT, which permits monitoring of response to treatment. Limitations are its nonspecificity for mild EPI [79], its complexity, and its limited availability.

Coefficient of Fat Absorption This is the gold standard for the diagnosis of steatorrhea, as it occurs in EPI. Patients are required to restrict their diet to 100 g of fat or less each day for five consecutive days. The total amount of feces produced over the last three days are collected and analyzed. A coefficient of fat absorption below 93% is considered abnormal [80]. Currently, the coefficient of fat absorption is the only test accepted by the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the indication and monitoring of PERT in clinical trials. Its main drawback is the lack of compliance by patients. Others include poor sensitivity for mild and moderate EPI and false-positive results in non-pancreatic fat malabsorption.

Serum Trypsinogen Levels of serum trypsinogen are associated with pancreatic acinar cell mass but it is not commonly employed in clinical practice.

Management of EPI

Every patient with CP should be screened for EPI. The reason for this is that it aids in the diagnosis of CP in patients without morphological features [81–84]. Also, the treatment of EPI has implications for clinical outcomes and survival [85–87]. In addition, even with unequivocal morphological findings of CP, the clinical symptoms of EPI are not always evident. Once diagnosed with CP, patients should be evaluated annually for EPI or when symptoms occur or deteriorate.

PERT is the mainstay of treatment for EPI. If symptoms are unclear, a therapeutic trial of PERT for four to six weeks can be helpful. Enteric-coated microspheres or minimicrospheres of less than 2 mm are the preparations of choice. Enzyme preparations are manufactured with a pH-sensitive enteric coating that protects them from acidic degradation in the stomach, allowing them to reach the duodenum [88–90].

A minimum lipase dose of 40 000–50 000 units is recommended with main meals, and half that dose with snacks. This recommendation is based on the notion that the initial dose should be about 10% of the physiologically secreted dose of lipase after a meal [91]. Adequate results have been obtained with doses ranging from 10 000 to 80 000 units per meal [23,92–94].

The improvement in symptoms has been classically tied to the success of PERT. However, symptom improvement does not necessarily correlate with correction of specific nutritional deficiencies. Therefore, both normalization of symptoms and nutritional parameters (biochemical and anthropometric) should be used to evaluate the efficacy of PERT [95,96]. In cases in which clinical improvement is not achieved, the dose can be increased. Doubling or tripling the dose has been anecdotally reported to be of use in patients with EPI, although not supported by any controlled study. Studies have reported the benefit of adding a proton pump inhibitor (PPI) to PERT [97,98].

If no improvement is seen despite increasing the dose of PERT and or adding a PPI, other causes should be investigated [43]. Effectiveness should not be evaluated using fecal elastase-1 measurements since this is a human enzyme that is not present in the commercially available pancreatin formulations.

Final Considerations

The management of patients with CP requires a meticulous and systematic approach. Ideally, a multidisciplinary team should be involved in the care of these patients. However, in certain scenarios this team may not be available. Therefore, we encourage clinicians to incorporate the checklist shown in Table 34.2 into their approach to patients with CP.

Table 34.2 Protocol for the approach to patients with CP.

Symptom/signs	Testing/assessment frequency	Diagnostic method(s)	Management
Pain	Every visit	Multidimensional pain scale(s)	PERT, antioxidants, NSAIDs, pregabalin, tramadol. Avoid opioids unless other agents fail or there is an exit strategy (endoscopic or surgical treatment)
Bone health	Every 1–2 years	DEXA scan, serum vitamin D levels	Vitamin D and calcium supplements
Diabetes	Annually or as dictated by signs/symptoms	FPG, HbA_{1c}, PP deficiency test if diagnosis is equivocal	PERT optimization, diet and exercise. Insulin therapy (ideally managed by nutritionist and endocrinologist), metformin. Avoid other glucose-lowering agents
EPI	Every visit	Indirect tests preferred due to availability (i.e. fecal elastase). If diagnosis remains equivocal, use direct tests if available. Serum albumin, retinol-binding protein, prealbumin/transthyretin, fat-soluble vitamins (A, D, E and K), zinc and magnesium as needed	PERT, nutritionist support if needed

Follow-up appointments every one to three months are appropriate if new patient or trying to control a specific aspect of CP. Once stable, visits can be scheduled every six months. Smoking and alcohol cessation should be reinforced at every visit.
DEXA, dual-energy X-ray absorptiometry; FPG, fasting plasma glucose; NSAIDs, nonsteroidal anti-inflammatory drugs; PERT, pancreatic enzyme replacement therapy; PP, pancreatic polypeptide.

Conclusion

The natural history of CP is highly variable due to the multitude of factors that intervene in its development. Clinicians should not only possess adequate knowledge about the condition itself and its multiple manifestations, but should maintain a high suspicion of it and routinely test patients who may be at risk according to their profiles. Establishing a timely diagnosis has the potential to provide a better therapeutic window that can impact the patient's quality of life and survival.

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