Chronic Pancreatitis

CHI Formulary Development Project

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Council of Health Insurance

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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Abbreviations

ACG	American College of Gastroenterology
CHI	Council of health insurance
CP	Chronic Pancreatitis
CPB	Celiac plexus block
CPRD	Chronic Pancreatitis related diabetes
CT	Computed tomography
DM	Diabetes mellitus
DXA	dual-energy X-ray absorptiometry
ERCP	Endoscopic retrograde cholangio-pancreatography
ESGE	European Society of Gastrointestinal Endoscopy
ESWL	Extracorporeal shockwave lithotripsy
EUS	Endoscopic ultrasonography
FPG	Fasting plasma glucose.
GLP-1RA	Glucagon-like peptide 1 receptor agonists
HOMA-B	Homeostasis model assessment of beta cells
IDF	Insurance drug formulary
MPD	Main Pancreatic duct
MRI	Magnetic Resonance Imaging
PEI	Pancreatic exocrine insufficiency
PERT	Pancreatic enzyme replacement therapy
PFC	Pancreatic fluid collection
SEMS	Self-expandable metallic stent
SGLT2i	Sodium-glucose cotransporter-2 (SGLT2) inhibitors
s-MRCP	secretin-enhanced magnetic resonance cholangiopancreatography
WHO	World health organization

Executive Summary

Chronic pancreatitis (CP) is a gradually worsening inflammatory condition that results in the permanent deterioration of the exocrine and endocrine tissues in the pancreas due to either atrophy or the substitution of fibrous tissue. This condition leads to significant outcomes such as intense abdominal pain, diabetes mellitus, and impaired nutrient absorption[1]. Chronic pancreatitis is also associated with an increased risk of pancreatic cancer[2].

Approximately 70% of chronic pancreatitis cases can be attributed to prolonged alcohol abuse, as extended periods of heavy drinking can repeatedly harm the pancreas. Less frequent factors include smoking, blocked or narrowed ducts of the pancreas, radiotherapy to the abdomen and genetics[3].

The goal of managing chronic pancreatitis treatment is to effectively regulate the condition and alleviate associated symptoms and it includes lifestyle modifications (avoiding alcohol, smoking cessation, dietary changes), enzyme supplementation, steroid medications, pain killers, and surgery for symptomatic chronic pancreatitis[3].

Chronic pancreatitis signs and symptoms can vary from upper abdominal pain, abdominal pain worsened by eating, unintentional weight loss, and steatorrhea[4].

Pancreatitis is divided into two: acute pancreatitis which is a sudden inflammation of the pancreas, often caused by gallstones or excessive alcohol consumption. It is characterized by a short-term, severe inflammatory response in the pancreas. Chronic pancreatitis, on the other hand, is a long-term inflammation of the pancreas that leads to permanent damage. It is typically associated with ongoing inflammation, fibrosis, and dysfunction of the pancreas over an extended period[5]. In this report, we will be focusing on the management of **chronic pancreatitis**.

Groove pancreatitis is a rare variant of chronic pancreatitis that impacts the area known as the 'groove' situated between the pancreatic head, duodenum, and common bile duct. While the precise etiology remains unidentified, it is notably linked to prolonged alcohol consumption, functional blockage of the Santorini duct, and Brunner glands hyperplasia[6].

Treatment for chronic pancreatitis typically involves a combination of pharmacological and surgical approaches, with a focus on pain management and addressing pancreatic insufficiency. The first-line treatment for pain management in chronic pancreatitis involves non-prescription pain relievers like ibuprofen and acetaminophen for mild pain and opioids or other prescription medications for severe pain. Pancreatic Enzyme Replacement Therapy (PERT) consists of enzyme supplements often prescribed to improve digestion and reduce pain. These enzymes help compensate for the lack of natural digestive enzymes produced by the damaged pancreas. Surgery is considered when medical management doesn't

provide relief from pain or complications like pancreatic pseudocysts, bile duct obstructions, or biliary strictures develop. Common surgical procedures include: Pancreatic Drainage Procedures (open blocked pancreatic ducts or remove pseudocysts), pancreatectomy (for severe cases, partial or total removal of the pancreas may be necessary). The choice between surgery and pharmacotherapy depends on the individual patient's condition, the severity of their symptoms, and the response to initial treatments. Surgery is typically reserved for cases where pain is debilitating, complications arise, or there is a significant loss of pancreatic function. In many cases, a combination of both surgical and pharmacological approaches may be necessary to effectively manage chronic pancreatitis[3].

Accurate population-based assessments of chronic pancreatitis epidemiology are not readily accessible due to substantial variations in diagnostic criteria. Nonetheless, the available limited data indicates that chronic pancreatitis incidence falls within a range of 5 to 12 cases per 100,000 individuals, with an estimated prevalence of around 50 cases per 100,000 persons[7]. No accurate statistics concerning the epidemiology of chronic pancreatitis in Saudi Arabia are available.

CHI issued Chronic Pancreatitis clinical guidance after thorough review of renowned international and national clinical guidelines in April 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Chronic Pancreatitis clinical guidance and seeks to offer guidance for the effective management of chronic pancreatitis. It provides an **update on the Chronic Pancreatitis Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, by being the **update** of the American College of Gastroenterology (ACG) Clinical Guideline: Chronic Pancreatitis in **2020.** The addition of **new guidelines to the report** such as AGA Clinical Practice Update on the Endoscopic Approach to Recurrent Acute and Chronic Pancreatitis: Expert Review **2022,** Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Updated August **2018,** International consensus guidelines on interventional endoscopy in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club **2020,** International consensus guidelines for surgery and the timing of intervention in chronic pancreatitis **2019,** United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis **2018,** International consensus guidelines on surveillance for

pancreatic cancer in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club **2020,** and the Guidelines for the diagnosis and treatment of chronic pancreatitis in China (**2018** edition).

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is advisable to make sure that Acemetacin (NSAID) was withdrawn from SFDA: other NSAID alternatives are commonly found on the market, especially indomethacin that is SFDA registered, acemetacin being a carboxymethyl ester of indomethacin.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in Chronic Pancreatitis management.

Below is a table summarizing the major changes based on the different Chronic Pancreatitis guidelines used to issue this report:

Table 1. General Recommendations for the Management of Chronic Pancreatitis

Management of Chronic Pancreatitis	
General Recommendations	**Level of Evidence/Grade of Recommendation and reference**
Surgical intervention over endoscopic therapy in patients with obstructive CP for the long-term relief of pain if first-line endoscopic approaches to pancreatic drainage have been exhausted or unsuccessful, is recommended.	Strong recommendation, moderate quality of evidence[8]
Surgery early in the disease process of CP is favored over surgery in a more advanced stage of disease to achieve optimal long-term pain relief.	Quality assessment: moderate; Recommendation: strong; Agreement: strong (alpha-score 100%)[9]
<u>Treatment of diabetes</u>: In patients with diabetes, lifestyle changes are recommended with respect to diet and physical activities. For patients with suspected insulin resistance, metformin is the first choice if there is no contraindication. Other oral hypoglycemic drugs are not recommended because of significant adverse events. When oral drugs are ineffective, insulin	N/A[10]

treatment is the next step. In patients with severe malnutrition, insulin treatment is the first choice. Additionally, hypoglycemia should be avoided because CP patients with diabetes are more sensitive to insulin.	
Endoscopic treatment for pediatric CP: In teenagers, CP usually presents as episodes of abdominal pain. Compared with adults, pediatric patients have a lower prevalence of complications, including diabetes, steatorrhea, and bile duct stricture. Endoscopic treatment (ERCP, ESWL) can relieve abdominal pain effectively and reduce the incidence of pancreatitis with an effective rate of 50%–70%. The main complication of endoscopic treatment is postoperative acute pancreatitis, which is like that of adults. Endoscopic treatment of adolescent CP is safe and effective.	N/A[10]
Surgery is superior to endoscopy in terms of mid-term and long-term pain relief in patients with painful CP.	GRADE 2B, agreement[11]
Paracetamol is preferred over NSAIDs as level I analgesic due to its limited side effects. Tramadol is the preferred level II analgesic due to its efficacy and safety profile. Strong oral opioids, at the lowest possible dose, are indicated as level III analgesia; dose escalation and addiction should be avoided.	N/A[11]
Evaluation and treatment of osteoporosis in patients with CP: - Patients with CP are at high risk of developing osteoporosis and osteopenia (Grade 1A) and are at high risk of suffering a low trauma fracture (Grade 1B). - Basic preventative measures (adequate diet, particularly calcium and vitamin D intake, regular weight-bearing exercise, and smoking/alcohol avoidance) should be encouraged for all CP patients.	GRADE 1B, strong agreement[11]

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **Chronic Pancreatitis clinical and therapeutic management.**

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Chronic Pancreatitis report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the April 2020 CHI Chronic Pancreatitis Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines requiring revision	
Old versions	**Updated versions**
NICE guidelines for Pancreatitis: diagnosis and management (2018)	N/A*
American Family Physician guidelines on chronic pancreatitis diagnosis and treatment (2018)	N/A*
The American College of Gastroenterology (ACG) Clinical Guideline: Chronic Pancreatitis (2019)	N/A*
The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on clinical nutrition in acute and chronic pancreatitis (2020)	N/A*

**: No updated version available: the existing version is the most recent one and no further updates or revisions have been made or released.*

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Chronic Pancreatitis report, along with their recommendations.

Table 3. List of Additional Guidelines

Additional Guidelines
AGA Clinical Practice Update on the Endoscopic Approach to Recurrent Acute and Chronic Pancreatitis: Expert Review (2022)[12]
Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Updated August 2018 [13]
International consensus guidelines on interventional endoscopy in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club (2020)[14]
International consensus guidelines for surgery and the timing of intervention in chronic pancreatitis (2019)[9]
United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (2018)[11]
International consensus guidelines on surveillance for pancreatic cancer in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club (2020)[15]
Guidelines for the diagnosis and treatment of chronic pancreatitis in China (2018 edition)[10]

1.2.1 AGA Clinical Practice Update on the Endoscopic Approach to Recurrent Acute and Chronic Pancreatitis: Expert Review (2022)

The American Gastroenterological Association (AGA) published its clinical practice update on the endoscopic approach to recurrent pancreatitis with the aim of providing practical and evidence-based guidance to clinicians regarding the role of endoscopy in both acute and chronic pancreatitis[12]. The main recommendations related to chronic pancreatitis are listed below.

- **Surgical intervention** should be considered over endoscopic therapy for long-term treatment of patients with painful obstructive chronic pancreatitis. Endoscopic intervention is a reasonable alternative to surgery for suboptimal operative candidates or those who favor a less invasive approach, assuming they are clearly informed that the best practice advice primarily favors surgery.
- When endoscopic retrograde cholangiopancreatography (ERCP) is pursued, small (≤ 5mm) main pancreatic duct stones can be treated with pancreatography and conventional stone extraction maneuvers. For larger stones, extracorporeal shockwave lithotripsy and/or pancreatoscopy with intraductal lithotripsy may be required.
- When ERCP is pursued, prolonged stent therapy (6–12 months) is effective for treating symptoms and remodeling main pancreatic duct strictures. The preferred approach is to place and sequentially add multiple plastic stents in parallel.
- ERCP with stent insertion is the preferred treatment for benign biliary stricture due to chronic pancreatitis. Fully covered self-expandable metal stents (FCSEMS) placement is favored over multiple plastic stents whenever feasible, given similar efficacy but significantly reduced need for stent exchange procedures during the treatment course.
- Celiac plexus block (CPB) should not be routinely performed for the management of pain due to chronic pancreatitis. The decision to proceed with CPB in selected patients with debilitating pain in whom other therapeutic measures have failed can be considered on a case by-case basis, but only after discussion of the unclear outcomes of this intervention and its procedural risks.

1.2.2 Endoscopic Treatment of Chronic Pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Updated August 2018

The ESGE published its 2018 update on the 2012 clinical guidelines for the endoscopic treatment of chronic pancreatitis[13]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was adopted to define the strength of recommendation and the quality of evidence (tables 4 and 5).

Table 4. GRADE Strengths of Recommendations

Strength of Recommendation	Definition
Strong	Very certain that benefits outweigh risks and burdens.
Weak	Risks and burdens appear to be finely balanced, or when benefits, risks, and burdens are closely balanced or uncertain.
Conditional	In between strong and weak recommendation.

Table 5. GRADE Levels of Evidence

Level of Evidence	Definition
High	(Very) low probability of further research substantially changing the conclusions.
Moderate	Further research might completely change the conclusions.
Low	Further research was likely to completely change the conclusions.

- **Endoscopic therapy** and/or **extracorporeal shockwave lithotripsy (ESWL)** is suggested as the **first-line** therapy for painful uncomplicated CP with an obstructed main pancreatic duct (MPD) in the head/body of the pancreas. The clinical response should be evaluated at 6 – 8 weeks; if it appears unsatisfactory, the patient's case should be discussed again in a multidisciplinary team and surgical options should be considered. *Weak recommendation, low quality evidence*.
- ESWL for the clearance of radiopaque obstructive MPD stones larger than 5mm located in the head/body of the pancreas and endoscopic retrograde cholangiopancreatography (ERCP) for MPD stones that are radiolucent or smaller than 5mm is recommended. *Strong recommendation, moderate quality evidence*.
- Restricting the use of endoscopic therapy after ESWL to patients with no spontaneous clearance of pancreatic stones after adequate fragmentation by ESWL is suggested. *Weak recommendation, moderate quality evidence*.
- Endoscopic drainage over percutaneous or surgical treatment for uncomplicated chronic pancreatitis (CP)-related pseudocysts that are within endoscopic reach is recommended. *Strong recommendation, moderate quality evidence*.

1.2.3 International Consensus Guidelines on Interventional Endoscopy in Chronic Pancreatitis. Recommendations from the Working Group for the International Consensus Guidelines for Chronic Pancreatitis in Collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club (2020)

Multidisciplinary experts from the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club (IAP-APA-JPS-EPC) jointly published in 2020 the International Consensus Guidelines on Chronic Pancreatitis (ICGCP). This paper aimed to be part of the international consensus guidelines on chronic pancreatitis, presenting for interventional endoscopy[14]. The GRADE approach was used to evaluate the level of evidence per statement (tables 4 and 5 above). The main recommendations are detailed below.

Indications for intervention in chronic pancreatitis

- Endoscopic or surgical treatment should be offered to patients with chronic pancreatitis with persistent severe pain. Intervention in the form of either surgery or endotherapy is not recommended in asymptomatic patients with chronic pancreatitis who do not have abdominal pain to improve pancreatic exocrine and/or endocrine function or prevent cancer. *(Quality assessment: moderate; Recommendation: strong; Agreement: strong)*
- Endoscopic or surgical treatment should be carried out after careful patient selection for local complications of chronic pancreatitis with persistent clinical symptoms such as gastric outlet obstruction, duodenal stenosis, biliary obstruction with cholestasis and pseudocysts. *(Quality assessment: moderate; Recommendation: strong; Agreement: strong)*
- Celiac plexus block may be undertaken in patients for significant abdominal pain who are not candidates for pancreatic surgery or have not responded to endotherapy and extracorporeal shock wave lithotripsy (ESWL) or have a poor general condition as a temporizing measure before definitive therapy. *(Quality assessment: moderate; Recommendation: weak; Agreement: weak)*

Treatment of pancreatic ductal stricture

- Non-surgical decompression of the main pancreatic duct including endoscopic therapy can be selected for immediate pain relief of chronic pancreatitis before considering surgery. Surgical intervention should be considered if endoscopic procedure fails or has temporary success needing

repeated endoscopic therapy. *(Quality assessment: moderate; Recommendation: conditional; Agreement: strong)*

- If there are contraindications for surgical therapy in patients in whom conventional endoscopic therapy has failed, endosonographic-guided drainage of the pancreatic duct is another option for pain control. *(Quality assessment: moderate; Recommendation: weak; Agreement: weak)*
- Endoscopic drainage should be the preferred modality for treating pancreatic pain and biliary stricture in patients with chronic pancreatitis who have associated portal/ splenic vein thrombosis. *(Quality assessment: moderate; Recommendation: conditional; Agreement: strong)*

Endoscopic stent treatment for pancreatic ductal stricture

- A straight plastic pancreatic stent should be placed across the stricture depending on the caliber of the stricture of the pancreatic duct. *(Quality assessment: low; Recommendation: conditional; Agreement: strong)*
- An ERCP inserted endoscopic stent should be removed or exchanged between 2 and 3 months later. At this time a new stent should be inserted if there is still a significant stricture. *(Quality assessment: low; Recommendation: conditional; Agreement: strong)*
- Multiple stents or a metal stent may be considered for persisting pancreatic strictures due to severe chronic pancreatitis. *(Quality assessment: low; Recommendation: conditional; Agreement: weak)*

Treatment of pancreatic ductal stones

- ESWL should be the first-line therapy as nonsurgical intervention for main pancreatic duct stones in patients with chronic pancreatitis who do not get adequate pain relief with conservative management although a stent placement may be done first to relieve pain. *(Quality assessment: low; Recommendation: conditional; Agreement: conditional)*
- Endoscopic extraction is indicated for small stones or stone fragments after ESWL. *(Quality assessment: moderate; Recommendation: conditional; Agreement: strong)*

Treatment of pancreatic pseudocysts in chronic pancreatitis

- For pancreatic pseudocysts that cause symptoms and/or complications, interventional or surgical treatment should be performed. *(Quality assessment: moderate; Recommendation: strong; Agreement: strong)*

- Underlying stricture or disruption of the main pancreatic duct with symptoms and/or complications should be treated with endoscopic transpapillary placement of a pancreatic stent for pseudocysts.
- Asymptomatic and uncomplicated pancreatic pseudocysts of more than 5 cm in diameter that do not resolve within six weeks may be treated with transmural drainage. *(Quality assessment: low; Recommendation: weak; Agreement: weak)*
- In case of a suspected neoplastic cystic lesion diagnostic needle aspiration of the cyst may be done. *(Quality assessment: low; Recommendation: weak; Agreement: weak)*
- Surgical intervention should be considered if endoscopic drainage of pseudocysts fails or has temporary success needing repeated endoscopic therapy, especially when there is disconnected duct syndrome, inflammatory mass, and intraductal calculi with duct strictures. *(Quality assessment: low; Recommendation: conditional; Agreement: strong)*

Treatment of distal main biliary duct obstruction in chronic pancreatitis

- Endoscopic treatment is recommended when the patients show symptoms related to the distal bile duct obstruction (obstructive jaundice and/or acute cholangitis), and in persistent cholestasis with alkaline phosphatase elevation (>2-3 times) for at least month even in asymptomatic patients. *(Quality assessment: low; Recommendation: conditional; Agreement: strong)*
- Endoscopic treatment with multiple plastic or covered metal stents may be effective for relieving of the symptoms related to the distal bile duct obstruction due to chronic pancreatitis. *(Quality assessment: low; Recommendation: weak; Agreement: conditional)*
- In main biliary duct strictures caused by chronic pancreatitis, biliary stent placement is recommended for a period of 6 months to 1 year. *(Quality assessment: low; Recommendation: weak; Agreement: Weak)*
- Plastic stent replacement for main biliary duct stricture is recommended every 3 months. The optimal period for replacement of covered metal stent is currently unknown. *(Quality assessment: low; Recommendation: weak; Agreement: Conditional)*
- Endoscopic placement of multiple plastic or covered metal stent and/or surgery are appropriate to manage refractory bile duct obstruction. *(Quality assessment: low; Recommendation: conditional; Agreement: conditional)*
- Surgical treatment should be planned if bile duct obstruction reoccurs after one year of endoscopic stent treatment. For the patients who have significant

calcifications and/or mass of the pancreatic head, surgical treatment may be preferred as an initial treatment. *(Quality assessment: low; Recommendation: strong; Agreement: strong)*

Treatment of internal pancreatic fistula and pancreatic pleural effusion and ascites in chronic pancreatitis

- Endoscopic interventional therapy should be undertaken for the management of internal pancreatic fistula in patients presenting with main pancreatic duct disruption or obstruction. *(Quality assessment: low; Recommendation: conditional; Agreement: Strong)*

Treatment of hemosuccus pancreaticus in chronic pancreatitis

- Percutaneous endovascular treatment should be the first choice of treatment for hemosuccus pancreaticus in hemodynamically stable patients. However, patients with hemodynamic instability and unsuccessful embolization should undergo surgery. *(Quality assessment: low; Recommendation: conditional; Agreement: strong)*

Treatment of duodenal obstruction in chronic pancreatitis

- Surgical treatment is recommended for duodenal stenosis associated with chronic pancreatitis, as endoscopic treatment is difficult in such cases. *(Quality assessment: moderate; Recommendation: conditional; Agreement: strong)*
- Duodenal stenosis due to chronic pancreatitis should be carefully differentiated from pancreatic cancer. *(Quality assessment: moderate; Recommendation: strong; Agreement: strong)*

1.2.4 International Consensus Guidelines for Surgery and the Timing of Intervention in Chronic Pancreatitis (2019)

An international working group with 15 experts on CP surgery from the major pancreas societies evaluated 20 statements generated from evidence on 5 questions deemed to be the most clinically relevant in CP. The GRADE approach was used to evaluate the level of evidence available for each statement[9]. The main recommendations are detailed below.

Indication for surgery in CP:

- The most common indication for surgery for CP is intractable pain. Quality assessment: high; Recommendation: strong; Agreement: strong (alpha-score 86%).

- Other indications for surgery are a suspicion of neoplasm Quality assessment: high; Recommendation: strong; Agreement: strong (alpha-score 100%).
- Other indications for surgery are local complications of adjacent organs, such as duodenal or common bile duct stenosis, pseudoaneurysm or erosion of the large vessels, large pancreatic pseudocysts and internal pancreatic fistula. Quality assessment: moderate; Recommendation: conditional; Agreement: strong (alpha-score 86%).

Optimal timing of surgery:

- Surgery early in the disease process of CP is favored over surgery in a more advanced stage of disease to achieve optimal long-term pain relief. Quality assessment: moderate; Recommendation: strong; Agreement: strong (alpha-score 100%)
- The risk of developing pancreatic exocrine insufficiency is lower after early surgery for CP than after surgery performed in an advanced disease stage. Pancreatic resection techniques have a higher risk for PEI than drainage techniques. Quality assessment: low; Recommendation: conditional; Agreement: conditional (alpha-score 79%).
- Long-term quality of life is improved after early surgery (<3 years of onset) compared to surgery in a more advanced stage of disease Quality assessment: low; Recommendation: conditional; Agreement: conditional (alpha-score 79%).

Risk of pancreatic cancer in a patient with CP and role for prophylactic cancer surgery?

- Surgical resection should be chosen for a suspected malignant cystic lesion. Quality assessment: high; Recommendation: strong; Agreement: strong (alpha-score 100%).
- The risk of pancreatic carcinoma is somewhat higher in patients with CP but still too low to recommend active screening or prophylactic surgery. Quality assessment: moderate; Recommendation: conditional; Agreement: strong (alpha-score 93%).

Patients with hereditary CP have such a high risk of pancreatic cancer that prophylactic resection can be considered. Quality assessment: moderate; Recommendation: conditional; Agreement: weak (alpha-score 57%).

1.2.5 United European Gastroenterology Evidence-Based Guidelines for the Diagnosis and Therapy of Chronic Pancreatitis (2017)

In collaboration with United European Gastroenterology, the working group on ‘Harmonizing diagnosis and treatment of chronic pancreatitis across Europe’

(HaPanEU) developed these European guidelines. Twelve multidisciplinary review groups performed systematic literature reviews to answer predefined clinical questions. Recommendations were graded using the GRADE system, and are summarized below[11,16].

- Surgical treatment has no role in asymptomatic and uncomplicated CP.
- Surgery is superior to endoscopy in terms of mid-term and long-term pain relief in patients with painful CP. (GRADE 2B, agreement)
- Early surgery is favored over surgery at a more advanced stage of the disease in terms of optimal long-term pain relief, long-term improved QoL, and risk of postoperative PEI (GRADE 2B-2C, weak agreement). In addition, pancreatic resection techniques have a higher risk of PEI than drainage techniques. (GRADE 2C, weak agreement). No recommendation can be drawn from the evidence regarding the effect of early surgery on developing endocrine pancreatic function. (GRADE 2C, strong agreement).

Surgical treatment in patients with groove pancreatitis

- In patients with groove (paraduodenal) pancreatitis, the initial therapy should involve medical treatment; endoscopic drainage procedures may occasionally be helpful. If these approaches fail, the patient should be referred for surgery. (GRADE 2C, strong agreement).
- Surgery should be aimed at pain relief and/or complete pain resolution and should solve the patient's malnutrition status (body weight gain), on condition that the patient stops alcohol and drug abuse. (GRADE 2C, strong agreement)
- In expert hands, pancreaticoduodenectomy is the most suitable surgical option for patients with groove pancreatitis. (GRADE 2C, strong agreement).

Medical therapy for exocrine pancreatic insufficiency

- PERT is indicated for patients with CP and PEI in the presence of clinical symptoms or laboratory signs of malabsorption (nutritional deficiencies). An appropriate nutritional evaluation is recommended to detect signs of malabsorption. (GRADE 1A, strong agreement).
- Enteric-coated microspheres or mini-microspheres of < 2 mm in size are the preparations of choice for PEI. (GRADE 1B, strong agreement).
- Oral pancreatic enzymes should be distributed along with meals and snacks. (GRADE 1A, strong agreement).
- A minimum lipase dose of 40,000-50,000 Ph.U. (Eur.Ph.U. or USP) is recommended with main meals, and half that dose with snacks. (GRADE 1A, strong agreement).

Treatment of pain in CP

- Pain is the first presentation of CP in most patients. (GRADE 1B, strong agreement). There is no evidence that pain symptoms 'burn out' in all patients with ongoing CP. (GRADE 2C, moderate agreement). There is no convincing evidence that endocrine and exocrine pancreatic insufficiencies are associated with pain relief. (GRADE 2C, moderate agreement).
- Pain intensity and the pain pattern over time (constant vs intermittent pain) have been shown to reduce QoL in patients with CP. (GRADE 1A, strong agreement).
- Pancreatic (stones, strictures, inflammatory masses, PPC) and extra-pancreatic complications (e.g., peptic ulcer, gastrointestinal cancer) may contribute to pain in the individual patient and should be thoroughly investigated at the time of diagnosis and if pain symptoms are worsening. (GRADE 1B, strong agreement).
- Pain in CP should be assessed using a multidimensional approach, including evaluation of pain intensity, pain pattern (constant vs intermittent) and its impact on daily function and QoL. (GRADE 1B, strong agreement).

Medical therapeutic strategies for pain in CP

- Cessation of alcohol, and possibly smoking, improves pain in CP and is highly recommended. (GRADE 1B, moderate agreement).
- PERT is not recommended for pain treatment in CP, although it may have beneficial effects on abdominal discomfort related to PEI. (GRADE 1B, moderate agreement).
- Antioxidants are not generally recommended for pain treatment in CP. (GRADE 1B, moderate agreement).
- The standard guideline for medical analgesic therapy in CP follows the principles of the 'pain relief ladder' provided by the WHO. (Grade 1B, strong agreement).

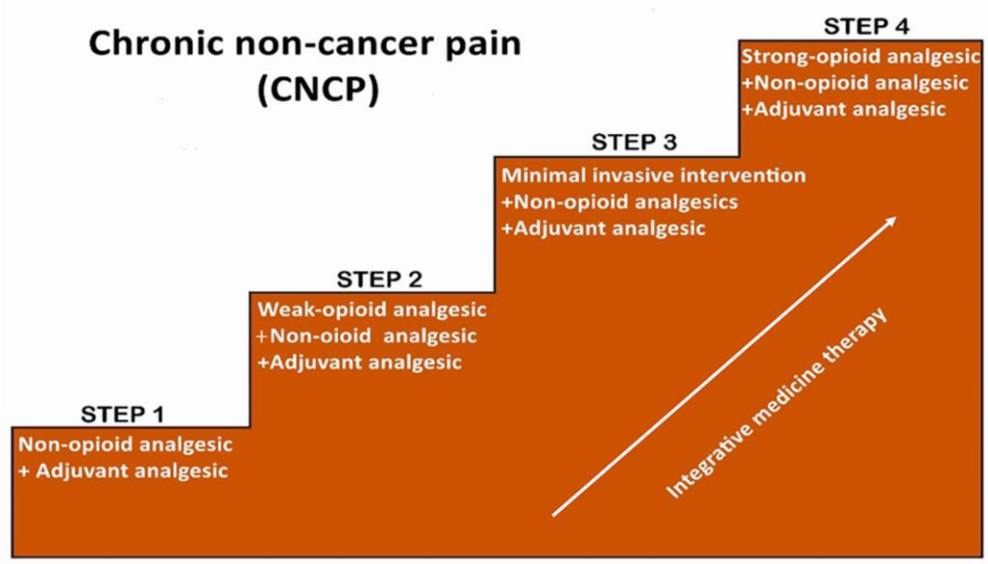

Figure 1. WHO Ladder for Pain Management[17]

- Paracetamol is preferred over NSAIDs as level I analgesic due to its limited side effects. Tramadol is the preferred level II analgesic due to its efficacy and safety profile. Strong oral opioids, at the lowest possible dose, are indicated as level III analgesia; dose escalation and addiction should be avoided.
- Adjuvant analgesics that can be used for pain in CP include low dose antidepressants, gabapentinoids (pregabalin) and anxiolytics.

    - **Endoscopic therapy for pain in CP**

- ET is effective in patients with an obstructive type of pancreatic pain and in patients with pancreatic duct dilatation. (GRADE 2C, moderate agreement). ET could be useful as a bridge to surgery. (GRADE 1B, moderate agreement). ET is less effective for pain in CP and has a shorter-term effect compared with surgery. (GRADE 1B, moderate agreement).
- ESWL therapy is effective for disintegrating stones in the main pancreatic duct and provides pain relief in patients with CP. (GRADE 2B-2C, weak agreement).

    - **Other nonsurgical treatments for pain in CP**

- Treatments such as EUS-guided plexus block, splanchnic nerve block, spinal cord stimulation, transcranial magnetic stimulation and acupuncture may be effective in selected cases of painful CP. (GRADE 1C, moderate agreement)

- **Nutrition:**
- Malnutrition is common among patients with CP. (GRADE 2B, strong agreement). PEI, anorexia secondary to abdominal pain, nausea and vomiting, alcohol and other substance abuse and diabetes mellitus may all contribute to malnutrition in patients with CP. (GRADE 2C, strong agreement).
- A physical examination should be performed and should include anthropometric measurements of mid-arm circumference, triceps skinfold and hand-grip strength. (GRADE 2B, moderate agreement). Screening for a deficiency of proteins, fat-soluble vitamins (A, D, E and K), zinc and magnesium should also be considered. (GRADE 2A, moderate agreement).

    - **Prevention and treatment of malnutrition**

- Patients who are well nourished should be encouraged to follow normal healthy eating advice. PEI should be corrected in those patients who are nutritionally compromised. Improved nutritional status can be achieved with nutritional assessment and individualized dietary counselling by an experienced dietician. (GRADE 1B, strong agreement)
- Dietary fat restriction and very high fiber diets should be avoided. (GRADE 1C strong agreement). Small, frequent, high-energy meals should be recommended for patients with malnutrition. (GRADE 2C strong agreement). Nutritional intervention should be carried out alongside pancreatic enzyme replacement therapy (PERT). (GRADE 2C, strong agreement).
- For most patients with CP, oral nutritional supplements are not required. For those who are undernourished and cannot meet their nutritional requirements orally despite dietary intervention, oral nutritional supplements may be useful. MCT supplements are not recommended. (GRADE 2C, strong agreement).
- Specific recommendations on the supplementation of vitamins A, E and K are not possible, nor it is possible to provide specific guidelines on dosage and administration methods, as there are few studies. Clinical evaluation is advised, along with adequate PERT and dietary intervention. (GRADE 1B, strong agreement).
- Vitamin D deficiency may be treated with oral supplementation or by a single intramuscular injection. (GRADE 2C, strong agreement).

    - **Evaluation and treatment of osteoporosis in patients with CP**

- Patients with CP are at high risk of developing osteoporosis and osteopenia (Grade 1A) and are at high risk of suffering a low trauma fracture (Grade 1B). (GRADE 1B, strong agreement). To identify those at risk, regular assessment of

bone density by dual-energy X-ray absorptiometry (DXA), along with regular measurement of serum 25(OH)-vitamin D should be undertaken. (GRADE 1C, strong agreement).

- Basic preventative measures (adequate diet, particularly calcium and vitamin D intake, regular weight-bearing exercise, and smoking/alcohol avoidance) should be encouraged for all CP patients. For those with osteopenia, basic preventative measures should be implemented and DXA should be repeated every two years. Patients with osteoporosis (or vertebral fractures) should receive appropriate medication, screening for other causes, and/or referral to a bone specialist, along with basic preventative measures. (GRADE 1C, strong agreement).

    - **Evaluation and treatment of diabetes mellitus in CP**

- The initial evaluation of a patient with CP should include fasting plasma glucose (FPG) and HbA1c. Criteria for a diagnosis of CPRD are FPG >= 126 mg/dL (7.0 mmoL/L) or HbA1c >= 6.5% (48 mmoL/mol). (GRADE 1A, strong agreement). An HbA1c <= 6.5% does not rule out CPRD due to the limitations of this test in this patient population. Therefore, normal HbA1c (< 6.5%) should always be confirmed by FPG. (GRADE 1B, strong agreement).
- An absent pancreatic polypeptide response to mixed-nutrient ingestion seems to be a specific indicator of CPRD as compared to the other types of diabetes. (GRADE 1C, strong agreement). Due to feasibility, this test is only recommended in cases of doubt. In patients with an established diagnosis of CP, diagnosis of CPRD can be based on the absence of type 1 DM-associated autoantibodies together with the presence of at least two of the following four criteria: impaired beta-cell function as evaluated by HOMA-B or C-peptide/glucose ratio, no excessive insulin resistance, impaired incretin (GIP or GLP-1) secretion, and fat-soluble vitamins and/or micronutrient deficiency.
- Treatment of CPRD should include efforts to promote lifestyle changes, which may improve glycemic control and minimize the risk of hypoglycemia. In patients with severe malnutrition, insulin therapy is commonly used as a first choice due to the desired anabolic effects of insulin in this special subset of patients. (GRADE 1C, strong agreement). If hyperglycemia is mild and concomitant insulin resistance is additionally diagnosed or suspected, therapy with metformin may be a choice in the absence of contraindications. (GRADE 1C, strong agreement). Sulfonylureas, glinides, thiazolidines, alpha-glycosidase inhibitors, incretin-based therapies, and sodium glucose co-transporter-2 (SGLT-2) should not be used for CPRD due to risk of hypoglycemia and prominent side effects.

- Ensuring adequate and appropriate PERT is essential for diabetes therapy in patients with CP. (GRADE 1C, strong agreement).

1.2.6 International Consensus Guidelines on Surveillance for Pancreatic Cancer in Chronic Pancreatitis. Recommendations from the Working Group for the International Consensus Guidelines for Chronic Pancreatitis in Collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club (2020)

The international group evaluated 10 statements generated from evidence on 5 questions relating to pancreatic cancer in CP. The GRADE approach was used to evaluate the level of evidence available per statement[15]. The main recommendations are listed below.

- The prevalence of pancreatic cancer in sporadic chronic pancreatitis is not high enough to justify screening or surveillance. (Quality assessment: high; recommendation: conditional.)

Best available surveillance methods

- The best available surveillance methods are CT and MRI. (Quality assessment: weak; recommendation: conditional; agreement)
- EUS should not be used for surveillance as early tumors may be obscured by inflammation, fibrosis, and calcification. (Quality assessment: moderate; recommendation: weak; agreement)
- Surveillance for pancreatic cancer in patients with hereditary pancreatitis due to PRSS1 mutations should be undertaken in pancreatic specialist centers. (Quality assessment: low; recommendation: strong; agreement)
- Surveillance should only be introduced after the age of 40 years and stopped when the patient would no longer be suitable for surgical intervention. (Quality assessment: moderate; recommendation: strong; agreement.)
- Patients should be advised to avoid use of tobacco, not drink alcohol, have a balanced healthy diet containing daily fruit and vegetables with a high folate intake, whilst moderating the intake of red meat and taking some form of regular high physical exercise, altogether aiming to avoid obesity. (Quality assessment: moderate; recommendation: strong; agreement.)

1.2.7 Guidelines for the Diagnosis and Treatment of Chronic Pancreatitis in China (2018 Edition)

The Chronic Pancreatitis Group of China organized over 80 experts of Gastroenterology, Biliary and Pancreatic Surgery, Endocrinology, Radiology and Pathology to revise and update the Chinese Guidelines for the Diagnosis and Treatment of Chronic Pancreatitis (2012 edition). The new guidelines are based on the latest medical evidence from China and other countries[10]. Recommendations are detailed below:

The main principles of treatment for CP are to eliminate the causative factors, relieve symptoms, improve pancreatic functions, decrease complications, and improve the patient's quality of life.

Basic Management:

CP patients are supposed to abstain from alcohol and smoking, avoid an excessive high-fat and high-protein diet, and exercise properly.

Medical therapy:

- Treatment of pancreatic exocrine insufficiency
    - Oral pancreatic enzyme replacement therapy (PERT) is the first choice for treatment of pancreatic exocrine insufficiency. Clinically, an enteric-coated pancreatin, containing a highly active lipase, may be chosen. The addition of a proton pump inhibitor or a histamine type-2 receptor antagonist is helpful to improve fat digestion in patients with an unsatisfactory response to PERT. For patients with malnutrition, a proper diet plus PERT is recommended. Supplement of medium-chain triglycerides may be optional, if necessary. When fat-soluble vitamins are insufficient, vitamin D should be supplemented appropriately.
- Treatment of diabetes
    - In patients with diabetes, it is recommended to change the lifestyle with respect to diet and physical activities. For patients with suspected insulin resistance, metformin is the first choice if there is no contraindication. Other oral hypoglycemic drugs are not recommended because of significant adverse events. When oral drugs are ineffective, insulin treatment is the next step. In patients with severe malnutrition, insulin treatment is the first choice. Additionally, hypoglycemia should be avoided because CP patients with diabetes are more sensitive to insulin.

- Pain management
    - PERT, antioxidants, and somatostatin may be effective for pain relief. The standard guideline for analgesic therapy in CP should comply with the principles of the “pain relief ladder”, provided by the World Health Organization (WHO). Oral drugs are the first choice. Step one, acetaminophen is the preferred analgesic, one of the non-steroidal anti-inflammatory drugs, with a lower incidence of adverse effects in the digestive tract. Step two, we should choose weak opioids, such as tramadol. Step three, analgesics should be the strong opioids selected for treatment.
    - Endoscopic treatment is effective in patients with an obstructive type of pancreatic pain caused by pancreatic duct stenosis or stones in the pancreatic duct. Other interventional methods, such as CT or EUS-guided coeliac plexus block, are not recommended as routine therapy, with short episodes of pain relief and a high incidence of adverse events. Surgical treatment is optional when both medication and endoscopic therapy are ineffective. For CP patients with pain and main pancreatic duct dilatation, surgery is superior to endoscopic therapy in long-term pain relief.

The main indications for endoscopic treatments for CP include pancreatic duct stones, pancreatic duct stenosis, pancreatic pseudocysts, and bile duct stricture. Endoscopic treatments are beneficial to relieve abdominal pain and improve a patient’s quality of life.

- Endoscopic treatment for pediatric CP

    In teenagers, CP usually presents as episodes of abdominal pain. Compared with adults, pediatric patients have a lower prevalence of complications, including diabetes, steatorrhea, and bile duct stricture. Endoscopic treatment (ERCP, ESWL) can relieve abdominal pain effectively and reduce the incidence of pancreatitis with an effective rate of 50%–70%. The main complication of endoscopic treatment is postoperative acute pancreatitis, which is like that of adults. Endoscopic treatment of adolescent CP is safe and effective.

- Surgical therapy Indications
    - Patients should consider surgical therapy under the following conditions:
        - (i) intractable pain that cannot be alleviated by conservative treatment or endoscopic treatment.

- (ii) complicated by biliary obstruction, duodenal obstruction, pancreatic pseudocyst, pancreatic portal hypertension with hemorrhage, pancreatic fistula, pancreatic ascites, or pseudoaneurysm, and not suitable or ineffective for medical and interventional treatment.
- (iii) suspected malignancy
- (iv) failed endoscopic treatment.

Section 2.0 Drug Therapy

This section comprises three subsections: the first one contains the newly recommended drugs SFDA registered, the second one covers drug modifications, the third one outlines the drugs that have been withdrawn from the market.

2.1 Additions

After April 2020, there have been no new drugs that have received FDA and EMA approval and are SFDA registered for Chronic Pancreatitis treatment.

2.2 Modifications

No modifications were made to the drugs mentioned in the previous Chronic Pancreatitis.

2.3 Delisting

Please refer to section 2.1.6 of the previous CHI report.

Table 6. Delisting of Acemetacin

Drug	Class	NUPCO/ Special import	Place in therapy	Alternatives
Acemetacin	NSAID	No No	Treatment of pain due to chronic pancreatitis	Other NSAIDS, specifically indometacin because acemetacin is a carboxymethyl ester of indometacin

Section 3.0 Key Recommendations Synthesis

- Surgical intervention over endoscopic therapy in patients with obstructive CP for the long-term relief of pain if first-line endoscopic approaches to pancreatic drainage have been exhausted or unsuccessful, is recommended. (Strong recommendation, moderate quality of evidence)[8]

Treatment of pancreatic ductal stricture:

- Non-surgical decompression of the main pancreatic duct including endoscopic therapy can be selected for immediate pain relief of chronic pancreatitis before considering surgery. (Quality assessment: moderate Recommendation: conditional Agreement: strong)[14]

Treatment of pancreatic ductal stones:

- ESWL should be the first-line therapy as nonsurgical intervention for main pancreatic duct stones in patients with chronic pancreatitis who do not get adequate pain relief with conservative management although a stent placement may be done first to relieve pain. (Quality assessment: low Recommendation: conditional Agreement: conditional)[14]

Treatment of pancreatic pseudocysts in chronic pancreatitis:

- Asymptomatic and uncomplicated pancreatic pseudocysts of more than 5 cm in diameter that do not resolve within six weeks may be treated with transmural drainage. Quality assessment: low Recommendation: weak Agreement: weak[14]
- For pancreatic pseudocysts that cause symptoms and/or complications, interventional or surgical treatment should be performed. Quality assessment: moderate Recommendation: strong Agreement: strong[14]

Treatment of distal main biliary duct obstruction in chronic pancreatitis:

- In main biliary duct strictures caused by chronic pancreatitis, biliary stent placement is recommended for a period of 6 months to 1 year. Quality assessment: low Recommendation: weak Agreement: Weak[14]
- Plastic stent replacement for main biliary duct stricture is recommended every 3 months. The optimal period for replacement of covered metal stent is currently unknown. Quality assessment: low Recommendation: weak Agreement: Conditional[14]

Treatment of internal pancreatic fistula and pancreatic pleural effusion and ascites in chronic pancreatitis:

- Endoscopic interventional therapy should be undertaken for the management of internal pancreatic fistula in patients presenting with main

pancreatic duct disruption or obstruction. Quality assessment: low Recommendation: conditional Agreement: Strong[14]

Treatment of hemosuccus pancreaticus in chronic pancreatitis:

- Percutaneous endovascular treatment should be the first choice of treatment for hemosuccus pancreaticus in hemodynamically stable patients. However, patients with hemodynamic instability and unsuccessful embolization should undergo surgery. Quality assessment: low Recommendation: conditional Agreement: strong[14]

Surgical treatment in patients with groove pancreatitis:

- In patients with groove (paraduodenal) pancreatitis, the initial therapy should involve medical treatment; endoscopic drainage procedures may occasionally be helpful. If these approaches fail, the patient should be referred for surgery. (GRADE 2C, strong agreement)[18]

Medical therapeutic strategies for pain in CP:

- Paracetamol is preferred over NSAIDs as level I analgesic due to its limited side effects. Tramadol is the preferred level II analgesic due to its efficacy and safety profile. Strong oral opioids, at the lowest possible dose, are indicated as level III analgesia; dose escalation and addiction should be avoided[18]

Treatment of diabetes:

- In patients with diabetes, it is recommended to change the lifestyle with respect to diet and physical activities. For patients with suspected insulin resistance, metformin is the first choice if there is no contraindication. Other oral hypoglycemic drugs are not recommended because of significant adverse events. When oral drugs are ineffective, insulin treatment is the next step. In patients with severe malnutrition, insulin treatment is the first choice. Additionally, hypoglycemia should be avoided because CP patients with diabetes are more sensitive to insulin[10]

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Chronic Pancreatitis report** and aims to provide recommendations to aid in the management of Chronic Pancreatitis. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Chronic Pancreatitis. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Chronic Pancreatitis Scope

Section	Rationale/Updates
The American College of Gastroenterology (ACG) Clinical Guideline: Chronic Pancreatitis 2020 [8]	**Diagnosis of CP:** - Computed tomography (CT) or MRI for the first-line diagnosis of CP is recommended. Either test should be the first choice for the diagnosis of CP. Endoscopic ultrasonography (EUS), because of its invasiveness and lack of specificity, should be used only if the diagnosis is in question after cross-sectional imaging is performed (strong recommendation, low quality of evidence). - performing secretin-enhanced magnetic resonance cholangiopancreatography (s-MRCP) when the diagnosis of CP following cross-sectional imaging or EUS is not confirmed and the clinical suspicion remains high is suggested (conditional recommendation, low quality of evidence). - Histological examination as the gold standard to diagnose CP in high-risk patients when the clinical and functional evidence of CP is strong, but imaging modalities are inconclusive is suggested. (Conditional recommendation, very low quality of evidence) - Genetic testing in patients with clinical evidence of a pancreatitis-associated disorder or possible CP in which the etiology is unclear, especially in younger patients is recommended. (Strong recommendation, low quality of evidence) - Alcohol cessation in patients with CP is recommended (strong recommendation, very low quality of evidence). - Smoking cessation in patients with CP is recommended. (Strong recommendation, very low quality of evidence). - Surgical intervention over endoscopic therapy in patients with obstructive CP for the long-term relief of pain if first-line endoscopic approaches to pancreatic drainage have been exhausted or unsuccessful, is recommended. (Strong recommendation, moderate quality of evidence) ➔ All management-related recommendations are written in the previous report and no changes were made to these recommendations.
AGA Clinical Practice Update on the Endoscopic Approach to Recurrent Acute and Chronic Pancreatitis: Expert Review 2022 [12]	- Surgical intervention should be considered over endoscopic therapy for long-term treatment of patients with painful obstructive chronic pancreatitis. Endoscopic intervention is a reasonable alternative to surgery for suboptimal operative candidates or those who favor a less invasive approach, assuming they are clearly informed that the best practice advice primarily favors surgery. - When ERCP is pursued, small (<=5mm) main pancreatic duct stones can be treated with pancreatography and conventional stone extraction maneuvers. For larger stones, extracorporeal shockwave lithotripsy and/or pancreatoscopy with intraductal lithotripsy may be required. - When ERCP is pursued, prolonged stent therapy (6–12 months) is effective for treating symptoms and remodeling main pancreatic duct strictures. The preferred approach is to place and sequentially add multiple plastic stents in parallel (upsizing); emerging evidence suggests that fully covered self-expanding metal stents may have a role for this indication, but additional research is necessary. - ERCP with stent insertion is the preferred treatment for benign biliary stricture due to chronic pancreatitis. FCSEMS placement is favored over multiple plastic stents whenever feasible, given similar efficacy but significantly reduced need for stent exchange procedures during the treatment course.

	- Celiac plexus block should not be routinely performed for the management of pain due to chronic pancreatitis. The decision to proceed with celiac plexus block in selected patients with debilitating pain in whom other therapeutic measures have failed can be considered on a case by-case basis, but only after discussion of the unclear outcomes of this intervention and its procedural risks.
Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Updated August 2018[13]	- Endoscopic therapy and/or extracorporeal shockwave lithotripsy (ESWL) is suggested as the first-line therapy for painful uncomplicated chronic pancreatitis (CP) with an obstructed main pancreatic duct (MPD) in the head/body of the pancreas. The clinical response should be evaluated at 6 – 8 weeks; if it appears unsatisfactory, the patient's case should be discussed again in a multidisciplinary team and surgical options should be considered. Weak recommendation, low quality evidence. - Taking into consideration predictive factors associated with a good long-term outcome is suggested for the selection of patients for initial or continued endoscopic therapy and/or ESWL. These include, at initial work-up, absence of MPD stricture, a short disease duration, non-severe pain, absence, or cessation of cigarette smoking and of alcohol intake, and, after initial treatment, complete removal of obstructive pancreatic stones and resolution of pancreatic duct stricture with stenting. Weak recommendation, low quality evidence. - ESWL for the clearance of radiopaque obstructive MPD stones larger than 5mm located in the head/body of the pancreas and endoscopic retrograde cholangiopancreatography (ERCP) for MPD stones that are radiolucent or smaller than 5mm is recommended. Strong recommendation, moderate quality evidence. - Restricting the use of endoscopic therapy after ESWL to patients with no spontaneous clearance of pancreatic stones after adequate fragmentation by ESWL is suggested. Weak recommendation, moderate quality evidence. - Treating painful dominant MPD strictures with a single 10-Fr plastic stent for one uninterrupted year if symptoms improve after initial successful MPD drainage is suggested. The stent should be exchanged, if necessary, based on symptoms or signs of stent dysfunction at regular pancreas imaging at least every 6 months. ESGE suggests consideration of surgery or multiple side-by-side plastic stents for symptomatic MPD strictures persisting beyond 1 year after the initial single plastic stenting, following multidisciplinary discussion. Weak recommendation, low quality evidence. - Endoscopic drainage over percutaneous or surgical treatment for uncomplicated chronic pancreatitis (CP)-related pseudocysts that are within endoscopic reach is recommended. Strong recommendation, moderate quality evidence. - Retrieval of transmural plastic stents at least 6 weeks after pancreatic pseudocyst regression if MPD disruption has been excluded, and long-term indwelling of transmural double-pigtail plastic stents in patients with disconnected pancreatic duct syndrome is recommended. Strong recommendation, low quality evidence.
International consensus guidelines on interventional endoscopy	**Indications for intervention in chronic pancreatitis:** - Endoscopic or surgical treatment should be offered to patients with chronic pancreatitis with persistent severe pain. Intervention in the form of either surgery or endotherapy is not recommended in asymptomatic patients with chronic pancreatitis who do not have abdominal pain to improve pancreatic exocrine and/or endocrine function or prevent cancer. (Quality assessment: moderate Recommendation: strong Agreement: strong)

in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club 2020[14]	- Endoscopic or surgical treatment should be carried out after careful patient selection for local complications of chronic pancreatitis with persistent clinical symptoms such as gastric outlet obstruction, duodenal stenosis, biliary obstruction with cholestasis and pseudocysts. (Quality assessment: moderate Recommendation: strong Agreement: strong) - Celiac plexus block may be undertaken in patients for significant abdominal pain who are not candidates for pancreatic surgery or have not responded to endotherapy and extracorporeal shock wave lithotripsy (ESWL) or have a poor general condition as a temporizing measure before definitive therapy. (Quality assessment: moderate Recommendation: weak Agreement: weak) **Treatment of pancreatic ductal stricture:** - Non-surgical decompression of the main pancreatic duct including endoscopic therapy can be selected for immediate pain relief of chronic pancreatitis before considering surgery. Surgical intervention should be considered if endoscopic procedure fails or has temporary success needing repeated endoscopic therapy. Quality assessment: moderate Recommendation: conditional Agreement: strong - If there are contraindications for surgical therapy in patients in whom conventional endoscopic therapy has failed, endosonographic-guided drainage of the pancreatic duct is another option for pain control. Quality assessment: moderate Recommendation: weak Agreement: weak. - Endoscopic drainage should be the preferred modality for treating pancreatic pain and biliary stricture in patients with chronic pancreatitis who have associated portal/ splenic vein thrombosis. Quality assessment: moderate Recommendation: conditional Agreement: strong **Endoscopic stent treatment for pancreatic ductal stricture:** - A straight plastic pancreatic stent should be placed across the stricture depending on the caliber of the stricture of the pancreatic duct. Quality assessment: low Recommendation: conditional Agreement: strong - An endoscopic retrograde cholangio-pancreatography (ERCP) inserted endoscopic stent should be removed or exchanged at between 2 and 3 months later. At this time a new stent should be inserted if there is still a significant stricture. Quality assessment: low Recommendation: conditional Agreement: strong - Multiple stents or a metal stent may be considered for persisting pancreatic strictures due to severe chronic pancreatitis. Quality assessment: low Recommendation: conditional Agreement: weak **Treatment of pancreatic ductal stones:** - ESWL should be the first-line therapy as nonsurgical intervention for main pancreatic duct stones in patients with chronic pancreatitis who do not get adequate pain relief with conservative management although a stent placement may be done first to relieve pain. Quality assessment: low Recommendation: conditional Agreement: conditional - Endoscopic extraction is indicated for small stones or stone fragments after ESWL. Quality assessment: moderate Recommendation: conditional Agreement: strong **Treatment of pancreatic pseudocysts in chronic pancreatitis:**

	- For pancreatic pseudocysts that cause symptoms and/or complications, interventional or surgical treatment should be performed. Quality assessment: moderate Recommendation: strong Agreement: strong - Underlying stricture or disruption of the main pancreatic duct with symptoms and/or complications should be treated with endoscopic transpapillary placement of a pancreatic stent for pseudocysts. - Asymptomatic and uncomplicated pancreatic pseudocysts of more than 5 cm in diameter that do not resolve within six weeks may be treated with transmural drainage. Quality assessment: low Recommendation: weak Agreement: weak - In case of a suspected neoplastic cystic lesion diagnostic needle aspiration of the cyst may be done. Quality assessment: low Recommendation: weak Agreement: weak - Surgical intervention should be considered if endoscopic drainage of pseudocysts fails or has temporary success needing repeated endoscopic therapy, especially when there is disconnected duct syndrome, inflammatory mass, and intraductal calculi with duct strictures. Quality assessment: low Recommendation: conditional Agreement: strong **Treatment of distal main biliary duct obstruction in chronic pancreatitis:** - Endoscopic treatment is recommended when the patients show symptoms related to the distal bile duct obstruction (obstructive jaundice and/or acute cholangitis), and in persistent cholestasis with alkaline phosphatase elevation (>2-3 times) for at least month even in asymptomatic patients. Quality assessment: low Recommendation: conditional Agreement: strong - Endoscopic treatment with multiple plastic or covered metal stents may be effective for relieving of the symptoms related to the distal bile duct obstruction due to chronic pancreatitis. Quality assessment: low Recommendation: weak Agreement: conditional - In main biliary duct strictures caused by chronic pancreatitis, biliary stent placement is recommended for a period of 6 months to 1 year. Quality assessment: low Recommendation: weak Agreement: Weak - Plastic stent replacement for main biliary duct stricture is recommended every 3 months. The optimal period for replacement of covered metal stent is currently unknown. Quality assessment: low Recommendation: weak Agreement: Conditional - Endoscopic placement of multiple plastic or covered metal stent and/or surgery are appropriate to manage refractory bile duct obstruction. Quality assessment: low Recommendation: conditional Agreement: conditional - Surgical treatment should be planned if bile duct obstruction reoccurs after one year of endoscopic stent treatment. For the patients who have significant calcifications and/or mass of the pancreatic head, surgical treatment may be preferred as an initial treatment. Quality assessment: low Recommendation: strong Agreement: strong **Treatment of internal pancreatic fistula and pancreatic pleural effusion and ascites in chronic pancreatitis.** - Endoscopic interventional therapy should be undertaken for the management of internal pancreatic fistula in patients presenting with main pancreatic duct

	disruption or obstruction. Quality assessment: low Recommendation: conditional Agreement: Strong **Treatment of hemosuccus pancreaticus in chronic pancreatitis:** - Percutaneous endovascular treatment should be the first choice of treatment for hemosuccus pancreaticus in hemodynamically stable patients. However, patients with hemodynamic instability and unsuccessful embolization should undergo surgery. Quality assessment: low Recommendation: conditional Agreement: strong **Treatment of duodenal obstruction in chronic pancreatitis:** - Surgical treatment is recommended for duodenal stenosis associated with chronic pancreatitis, as endoscopic treatment is difficult in such cases. Quality assessment: moderate Recommendation: conditional Agreement: strong - Duodenal stenosis due to chronic pancreatitis should be carefully differentiated from pancreatic cancer. Quality assessment: moderate Recommendation: strong Agreement: strong
International consensus guidelines for surgery and the timing of intervention in chronic pancreatitis[9]	**Indication for surgery in CP:** - The most common indication for surgery for CP is intractable pain Quality assessment: high; Recommendation: strong; Agreement: strong (alpha-score 86%). - Other indications for surgery are a suspicion of neoplasm Quality assessment: high; Recommendation: strong; Agreement: strong (alpha-score 100%). - Other indications for surgery are local complications of adjacent organs, such as duodenal or common bile duct stenosis, pseudoaneurysm or erosion of the large vessels, large pancreatic pseudocysts and internal pancreatic fistula. Quality assessment: moderate; Recommendation: conditional; Agreement: strong (alpha-score 86%). **Optimal timing of surgery:** - Surgery early in the disease process of CP is favored over surgery in a more advanced stage of disease to achieve optimal long-term pain relief. Quality assessment: moderate; Recommendation: strong; Agreement: strong (alpha-score 100%) - The risk of developing pancreatic exocrine insufficiency is lower after early surgery for CP than after surgery performed in an advanced disease stage. Pancreatic resection techniques have a higher risk for PEI than drainage techniques. Quality assessment: low; Recommendation: conditional; Agreement: conditional (alpha-score 79%). - Long-term quality of life is improved after early surgery (<3 years of onset) compared to surgery in a more advanced stage of disease Quality assessment: low; Recommendation: conditional; Agreement: conditional (alpha-score 79%). **Risk of pancreatic cancer in a patient with CP and role for prophylactic cancer surgery?** - Surgical resection should be chosen for a suspected malignant cystic lesion. Quality assessment: high; Recommendation: strong; Agreement: strong (alpha-score 100%). - The risk of pancreatic carcinoma is somewhat higher in patients with CP but still too low to recommend active screening or prophylactic surgery. Quality

	assessment: moderate; Recommendation: conditional; Agreement: strong (alpha-score 93%). - Patients with hereditary CP have such a high risk of pancreatic cancer that prophylactic resection can be considered. Quality assessment: moderate; Recommendation: conditional; Agreement: weak (alpha-score 57%).
United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis 2018 [18]	- Surgical treatment has no role in asymptomatic and uncomplicated CP. - Surgery is superior to endoscopy in terms of mid-term and long-term pain relief in patients with painful CP. (GRADE 2B, agreement) - Early surgery is favored over surgery at a more advanced stage of the disease in terms of optimal long-term pain relief, long-term improved QoL, and risk of postoperative PEI (GRADE 2B-2C, weak agreement). In addition, pancreatic resection techniques have a higher risk of PEI than drainage techniques. (GRADE 2C, weak agreement). No recommendation can be drawn from the evidence regarding the effect of early surgery on developing endocrine pancreatic function. (GRADE 2C, strong agreement). **Surgical treatment in patients with groove pancreatitis:** - In patients with groove (paraduodenal) pancreatitis, the initial therapy should involve medical treatment; endoscopic drainage procedures may occasionally be helpful. If these approaches fail, the patient should be referred for surgery. (GRADE 2C, strong agreement). - Surgery should be aimed at pain relief and/or complete pain resolution and should solve the patient's malnutrition status (body weight gain), on condition that the patient stops alcohol and drug abuse. (GRADE 2C, strong agreement) - In expert hands, pancreaticoduodenectomy is the most suitable surgical option for patients with groove pancreatitis. (GRADE 2C, strong agreement). **Medical therapy for exocrine pancreatic insufficiency:** - PERT is indicated for patients with CP and PEI in the presence of clinical symptoms or laboratory signs of malabsorption (nutritional deficiencies). An appropriate nutritional evaluation is recommended to detect signs of malabsorption. (GRADE 1A, strong agreement). - Enteric-coated microspheres or mini-microspheres of < 2 mm in size are the preparations of choice for PEI. (GRADE 1B, strong agreement). - Oral pancreatic enzymes should be distributed along with meals and snacks. (GRADE 1A, strong agreement). - A minimum lipase dose of 40,000e50,000 Ph.U. (Eur.Ph.U. or USP) is recommended with main meals, and half that dose with snacks. (GRADE 1A, strong agreement). **Treatment of pain in CP:** - Pain is the first presentation of CP in most patients. (GRADE 1B, strong agreement). There is no evidence that pain symptoms 'burn out' in all patients with ongoing CP. (GRADE 2C, moderate agreement). There is no convincing evidence that endocrine and exocrine pancreatic insufficiencies are associated with pain relief. (GRADE 2C, moderate agreement). - Pain intensity and the pain pattern over time (constant vs intermittent pain) have been shown to reduce QoL in patients with CP. (GRADE 1A, strong agreement).

	- Pancreatic (stones, strictures, inflammatory masses, PPC) and extra-pancreatic complications (e.g., peptic ulcer, gastrointestinal cancer) may contribute to pain in the individual patient and should be thoroughly investigated at the time of diagnosis and if pain symptoms are worsening. (GRADE 1B, strong agreement). - Pain in CP should be assessed using a multidimensional approach, including evaluation of pain intensity, pain pattern (constant vs intermittent) and its impact on daily function and QoL. (GRADE 1B, strong agreement). o **Medical therapeutic strategies for pain in CP:** - Cessation of alcohol, and possibly smoking, improves pain in CP and is highly recommended. (GRADE 1B, moderate agreement). - PERT is not recommended for pain treatment in CP, although it may have beneficial effects on abdominal discomfort related to PEI. (GRADE 1B, moderate agreement). - Antioxidants are not generally recommended for pain treatment in CP. (GRADE 1B, moderate agreement). - The standard guideline for medical analgesic therapy in CP follows the principles of the 'pain relief ladder' provided by the WHO. (Grade 1B, strong agreement). - Paracetamol is preferred over NSAIDs as level I analgesic due to its limited side effects. Tramadol is the preferred level II analgesic due to its efficacy and safety profile. Strong oral opioids, at the lowest possible dose, are indicated as level III analgesia; dose escalation and addiction should be avoided. - Adjuvant analgesics that can be used for pain in CP include low dose antidepressants, gabapentinoids (pregabalin) and anxiolytics. o **Endoscopic therapy for pain in CP:** - ET is effective in patients with an obstructive type of pancreatic pain and in patients with pancreatic duct dilatation. (GRADE 2C, moderate agreement). ET could be useful as a bridge to surgery. (GRADE 1B, moderate agreement). ET is less effective for pain in CP and has a shorter-term effect compared with surgery. (GRADE 1B, moderate agreement). - ESWL therapy is effective for disintegrating stones in the main pancreatic duct and provides pain relief in patients with CP. (GRADE 2B-2C, weak agreement). o **Other nonsurgical treatments for pain in CP:** - Treatments such as EUS-guided plexus block, splanchnic nerve block, spinal cord stimulation, transcranial magnetic stimulation and acupuncture may be effective in selected cases of painful CP. (GRADE 1C, moderate agreement) - **Nutrition:** - Malnutrition is common among patients with CP. (GRADE 2B, strong agreement). PEI, anorexia secondary to abdominal pain, nausea and vomiting, alcohol and other substance abuse and diabetes mellitus may all contribute to malnutrition in patients with CP. (GRADE 2C, strong agreement). - A physical examination should be performed and should include anthropometric measurements of mid-arm circumference, triceps skinfold and hand-grip strength.

	(GRADE 2B, moderate agreement). Screening for a deficiency of proteins, fat-soluble vitamins (A, D, E and K), zinc and magnesium should also be considered. (GRADE 2A, moderate agreement). o **Prevention and treatment of malnutrition** - Patients who are well nourished should be encouraged to follow normal healthy eating advice. PEI should be corrected in those patients who are nutritionally compromised. Improved nutritional status can be achieved with nutritional assessment and individualized dietary counselling by an experienced dietician. (GRADE 1B, strong agreement) - Dietary fat restriction and very high fiber diets should be avoided. (GRADE 1C strong agreement). Small, frequent, high-energy meals should be recommended for patients with malnutrition. (GRADE 2C strong agreement). Nutritional intervention should be carried out alongside pancreatic enzyme replacement therapy (PERT). (GRADE 2C, strong agreement). - For most patients with CP, oral nutritional supplements are not required. For those who are undernourished and cannot meet their nutritional requirements orally despite dietary intervention, oral nutritional supplements may be useful. MCT supplements are not recommended. (GRADE 2C, strong agreement). - Specific recommendations on the supplementation of vitamins A, E and K are not possible, nor it is possible to provide specific guidelines on dosage and administration methods, as there are few studies. Clinical evaluation is advised, along with adequate PERT and dietary intervention. (GRADE 1B, strong agreement). - Vitamin D deficiency may be treated with oral supplementation or by a single intramuscular injection. (GRADE 2C, strong agreement). o **Evaluation and treatment of osteoporosis in patients with CP:** - Patients with CP are at high risk of developing osteoporosis and osteopenia (Grade 1A) and are at high risk of suffering a low trauma fracture (Grade 1B). (GRADE 1B, strong agreement). To identify those at risk, regular assessment of bone density by dual-energy X-ray absorptiometry (DXA), along with regular measurement of serum 25(OH)-vitamin D should be undertaken. (GRADE 1C, strong agreement). - Basic preventative measures (adequate diet, particularly calcium and vitamin D intake, regular weight-bearing exercise, and smoking/alcohol avoidance) should be encouraged for all CP patients. For those with osteopenia, basic preventative measures should be implemented and DXA should be repeated every two years. Patients with osteoporosis (or vertebral fractures) should receive appropriate medication, screening for other causes, and/or referral to a bone specialist, along with basic preventative measures. (GRADE 1C, strong agreement). o **Evaluation and treatment of diabetes mellitus in CP:** - The initial evaluation of a patient with CP should include fasting plasma glucose (FPG) and HbA1c. Criteria for a diagnosis of CPRD are FPG >= 126 mg/dL (7.0 mmoL/L) or HbA1c >= 6.5% (48 mmoL/mol). (GRADE 1A, strong agreement). An HbA1c <= 6.5% does not rule out CPRD due to the limitations of this test in this patient population. Therefore, normal HbA1c (< 6.5%) should always be confirmed by FPG. (GRADE 1B, strong agreement).

	- An absent pancreatic polypeptide response to mixed-nutrient ingestion seems to be a specific indicator of CPRD as compared to the other types of diabetes. (GRADE 1C, strong agreement). Due to feasibility, this test is only recommended in cases of doubt. In patients with an established diagnosis of CP, diagnosis of CPRD can be based on the absence of type 1 DM-associated autoantibodies together with the presence of at least two of the following four criteria: impaired beta-cell function as evaluated by HOMA-B or C-peptide/glucose ratio, no excessive insulin resistance, impaired incretin (GIP or GLP-1) secretion, and fat-soluble vitamins and/or micronutrient deficiency. - Treatment of CPRD should include efforts to promote lifestyle changes, which may improve glycemic control and minimize the risk of hypoglycemia. In patients with severe malnutrition, insulin therapy is commonly used as a first choice due to the desired anabolic effects of insulin in this special subset of patients. (GRADE 1C, strong agreement). If hyperglycemia is mild and concomitant insulin resistance is additionally diagnosed or suspected, therapy with metformin may be a choice in the absence of contraindications. (GRADE 1C, strong agreement). Sulfonylureas, glinides, thiazolidines, alpha-glycosidase inhibitors, incretin-based therapies, and sodium glucose co-transporter-2 (SGLT-2) should not be used for CPRD due to risk of hypoglycemia and prominent side effects. - Ensuring adequate and appropriate PERT is essential for diabetes therapy in patients with CP. (GRADE 1C, strong agreement).
International consensus guidelines on surveillance for pancreatic cancer in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of	- The prevalence of pancreatic cancer in sporadic chronic pancreatitis is not high enough to justify screening or surveillance. Quality assessment: high; recommendation: conditional. **Best available surveillance methods:** - The best available surveillance methods are CT and MRI. Quality assessment: weak; recommendation: conditional; agreement: (a ¼ 70%) - EUS should not be used for surveillance as early tumors may be obscured by inflammation, fibrosis, and calcification. Quality assessment: moderate; recommendation: weak; agreement: (a ¼ 52%) - Surveillance for pancreatic cancer in patients with hereditary pancreatitis due to PRSS1 mutations should be undertaken in pancreatic specialist centers. Quality assessment: low; recommendation: strong; agreement: (a ¼ 100%) - Surveillance should only be introduced after the age of 40 years and stopped when the patient would no longer be suitable for surgical intervention. Quality assessment: moderate; recommendation: strong; agreement: (a ¼ 97%) - Patients should be advised to avoid use of tobacco, not drink alcohol, have a balanced healthy diet containing daily fruit and vegetables with a high folate intake, whilst moderating the intake of red meat and taking some form of regular high physical exercise, altogether aiming to avoid obesity. Quality assessment: moderate; recommendation: strong; agreement: (a ¼ 91%)

Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club 2020 [15]	
Guidelines for the diagnosis and treatment of chronic pancreatitis in China (2018 edition)[10]	The main principles of treatment for CP are to eliminate the causative factors, relieve symptoms, improve pancreatic functions, decrease complications, and improve the patient's quality of life. Basic Management: CP patients are supposed to abstain from alcohol and smoking, avoid an excessive high-fat and high-protein diet, and exercise properly. Medical therapy: - Treatment of pancreatic exocrine insufficiency o Oral pancreatic enzyme replacement therapy (PERT) is the first choice for treatment of pancreatic exocrine insufficiency. Clinically, an enteric-coated pancreatin, containing a highly active lipase, may be chosen. The addition of a proton pump inhibitor or a histamine type-2 receptor antagonist is helpful to improve fat digestion in patients with an unsatisfactory response to PERT. For patients with malnutrition, a proper diet plus PERT is recommended. Supplement of medium-chain triglycerides may be optional, if necessary. When fat-soluble vitamins are insufficient, vitamin D should be supplemented appropriately. - **Treatment of diabetes** o In patients with diabetes, it is recommended to change the lifestyle with respect to diet and physical activities. For patients with suspected insulin resistance, metformin is the first choice if there is no contraindication. Other oral hypoglycemic drugs are not recommended because of significant adverse events. When oral drugs are ineffective, insulin treatment is the next step. In patients with severe malnutrition, insulin treatment is the first choice. Additionally, hypoglycemia should be avoided because CP patients with diabetes are more sensitive to insulin. - **Pain management** o PERT, antioxidants, and somatostatin may be effective for pain relief. The standard guideline for analgesic therapy in CP should comply with the principles of the "pain relief ladder", provided by the World Health Organization (WHO). Oral drugs are the first choice. Step one, acetaminophen is the preferred analgesic, one of the non-steroidal anti-inflammatory drugs, with a lower incidence of adverse effects in the digestive tract. Step two, we should choose weak opioids, such as tramadol. Step three, analgesics should be the strong opioids selected for treatment.

	○ Endoscopic treatment is effective in patients with an obstructive type of pancreatic pain caused by pancreatic duct stenosis or stones in the pancreatic duct. Other interventional methods, such as CT or EUS-guided coeliac plexus block, are not recommended as routine therapy, with short episodes of pain relief and a high incidence of adverse events. Surgical treatment is optional when both medication and endoscopic therapy are ineffective. For CP patients with pain and main pancreatic duct dilatation, surgery is superior to endoscopic therapy in long-term pain relief. The main indications for endoscopic treatments for CP include pancreatic duct stones, pancreatic duct stenosis, pancreatic pseudocysts, and bile duct stricture. Endoscopic treatments are beneficial to relieve abdominal pain and improve a patient's quality of life. - Endoscopic treatment for pediatric CP In teenagers, CP usually presents as episodes of abdominal pain. Compared with adults, pediatric patients have a lower prevalence of complications, including diabetes, steatorrhea, and bile duct stricture. Endoscopic treatment (ERCP, ESWL) can relieve abdominal pain effectively and reduce the incidence of pancreatitis with an effective rate of 50%–70%. The main complication of endoscopic treatment is postoperative acute pancreatitis, which is like that of adults. Endoscopic treatment of adolescent CP is safe and effective. **Surgical therapy Indications** ○ Patients should consider surgical therapy under the following conditions: ○ (i) intractable pain that cannot be alleviated by conservative treatment or endoscopic treatment. ○ (ii) complicated by biliary obstruction, duodenal obstruction, pancreatic pseudocyst, pancreatic portal hypertension with hemorrhage, pancreatic fistula, pancreatic ascites, or pseudoaneurysm, and not suitable or ineffective for medical and interventional treatment. ○ (iii) suspected malignancy ○ (iv) failed endoscopic treatment.

Appendix C. MeSH Terms PubMed

Query	Filters	Search Details	Results
(Pancreatitis, Chronic[MeSH Terms]) OR (Chronic Pancreatitis[MeSH Terms])	Guideline, in the last 5 years	("pancreatitis, chronic"[MeSH Terms]") AND ((y_5[Filter]) AND (guideline[Filter]))	17

Appendix D. Treatment Algorithm

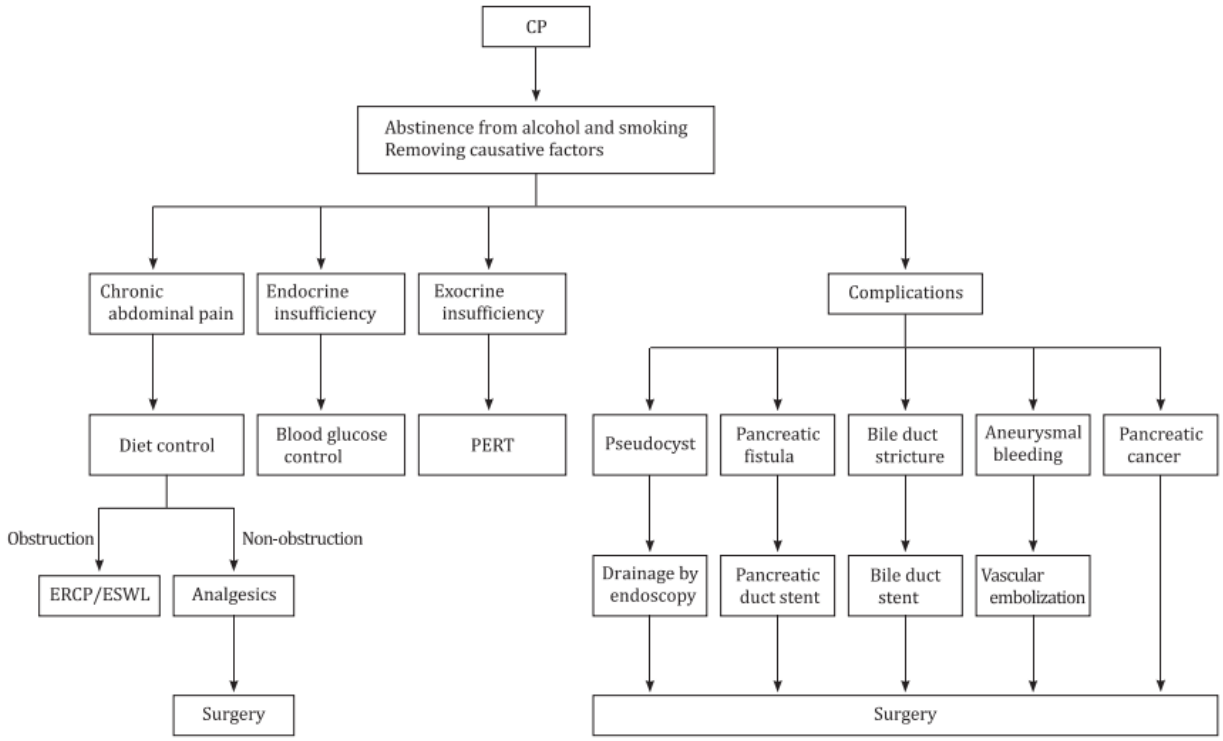

Figure 2. Treatment Algorithm for the Management of Chronic Pancreatitis

[1]

[1] Guidelines for the diagnosis and treatment of chronic pnacreatitis in China 2018 [10]