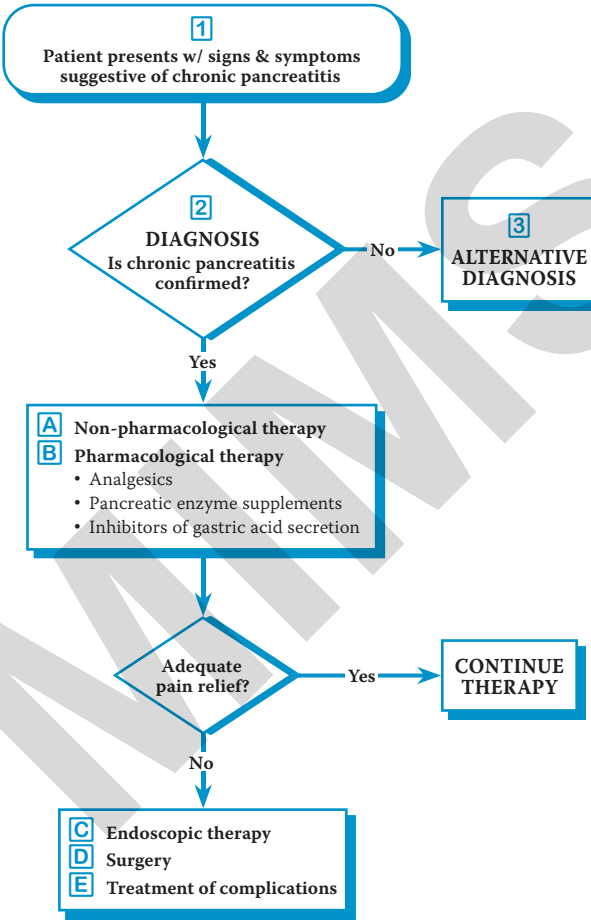
Pancreatitis - Chronic (1 of 9)



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1 CHRONIC PANCREATITIS

- Develops from irreversible scarring sustained by the pancreas from prolonged inflammation resulting in exocrine & endocrine dysfunction & increased risk of developing pancreatic ductal adenocarcinoma
- It is defined currently as a pathologic pancreatic inflammatory syndrome in persons w/ environmental, genetic &/or other risk factors who develop persistent pathologic responses to oxidative stress or injury to the parenchyma

Signs & Symptoms

Abdominal Pain

- Commonly epigastric in location which radiates to the back & frequently occurs at night or after meals
- Described as deep & piercing, may be associated w/ nausea & vomiting (N/V)
- Often severe, making it the most disabling clinical problem in patients w/ chronic pancreatitis
  - Severe pain may also lead to narcotic dependency
- May be relieved by sitting or leaning forward, assuming the knee-chest position on one side or by squatting & bringing the knees to the chest
- Causes decreased appetite leading to weight loss & malnutrition

Maldigestion & Steatorrhea (Exocrine Insufficiency)

- Symptoms of fat, protein & carbohydrate maldigestion become more apparent w/ advanced chronic pancreatitis following diminished digestive enzyme & bicarbonate secretion
- Diarrhea w/ bulky, foul-smelling or oily stools may be present
- Weight loss is not always seen even w/ maldigestion, but is more common during episodes of severe pain which markedly reduce food intake
  - In cases of considerable weight loss, investigate other causes eg pancreatic malignancy, small bowel bacterial overgrowth
- Malnutrition is common in patients w/ chronic pancreatitis & may be caused by abdominal pain, decreased food intake, diabetes mellitus (DM), pancreatic insufficiency, alcohol abuse & smoking
- Watery diarrhea, abdominal cramps & excess gas are uncommon

Development of Diabetes Mellitus (Endocrine Insufficiency)

- Chronic pancreatitis results in destruction of alpha & beta cells which gives rise to deficiencies of both glucagon & insulin
- Secondary diabetes results from the hormone deficiency

Causes of Chronic Pancreatitis

Alcohol

- Alcoholism has been found to be the foremost cause of chronic pancreatitis
- Recurrent attacks of acute alcoholic pancreatitis can lead to chronic pancreatitis

Smoking

- Smoking inhibits pancreatic bicarbonate secretion & reduces serum trypsin inhibitory capacity & alpha1-antitrypsin levels

Chronic Renal Failure

- Possible mechanisms of pancreatic injury from chronic renal failure:
  - Direct damage from uremic toxins
  - Changes in regulation of bicarbonate & protein secretion
- May lead to both acute & chronic pancreatitis

Hypercalcemia

- High levels of calcium may lead to trypsinogen activation & trypsin stabilization
- Explains the link between hyperparathyroidism & chronic pancreatitis

Other Causes

- Genetic polymorphisms, autoimmunity, recurrent attacks of acute pancreatitis

2 DIAGNOSIS

History

- Inquire about patient's past medical history (eg medication use, history of maldigestion/malnutrition, weight loss, or fractures, previous episodes of acute pancreatitis, DM, renal disease, & diseases associated w/ cystic fibrosis such as sinusitis, lung disease, or male infertility), family history (eg pancreatitis, pancreatic cancer, DM, cystic fibrosis), & social history (eg alcohol use, smoking)

Physical Exam

There is no physical exam finding that is specific for chronic pancreatitis

- Patients usually look well-nourished
- May note mild to moderate abdominal tenderness
- In severe disease, weight loss & malnutrition become more pronounced
- Other findings may include jaundice, a palpable abdominal mass which may be a pancreatic pseudocyst, a palpable spleen or signs of concurrent chronic alcoholic liver disease

2 DIAGNOSIS (CONT'D)

Pancreatic Function Tests

- Complementary tests in diagnosing exocrine pancreatic insufficiency in patients not yet diagnosed w/ chronic pancreatitis

Stool Elastase

- Easy to measure; level <100 mcg/g stool corresponds to advanced chronic pancreatitis
- Accurate in patients w/ steatorrhea, but less accurate in earlier disease

Stool Chymotrypsin

- Abnormal in most patients w/ advanced chronic pancreatitis & steatorrhea
- May be falsely positive in other malabsorptive conditions, severe malnutrition & diarrheal diseases that result in a dilute stool

Serum Trypsin

- Very low levels are specific for chronic pancreatitis, & may be seen in advanced disease w/ steatorrhea
- Inexpensive & risk-free, though not currently used due to poor correlation w/ imaging results & reports of elevated levels in nonpancreatic pain syndromes

Cholecystokinin (CCK) Stimulation Test

- Direct acinar cell function stimulation that measures trypsin &/or lipase
- Detects subtle exocrine pancreatic insufficiency
- Not readily available & requires specialized lab testing

Secretin Stimulation Test

- Direct ductal cell function stimulation that measures bicarbonate
- Damage to the pancreas may need to be substantial (30-50%) before tests become reliably positive
- Test is expensive, not readily available & prone to errors in measurement

Measurements of Pancreatic Enzyme Action

Fecal Fat

- Fat maldigestion arises when only about 10% of pancreatic lipase secretory capacity is left
- Test requires strict measurement of dietary fat & complete stool collection for 72 hours, which may make it difficult to perform

Bentiromide Test

- Urine metabolite used to measure chymotrypsin within the gut lumen, accurate only in advanced disease

Pancreolauryl Test

- Urine metabolite used to measure pancreatic arylesterases within the gut lumen, accurate only in advanced disease

Imaging Exams of the Pancreas

Abdominal X-rays

- Diffuse pancreatic calcifications are considered specific for chronic pancreatitis
  - Calcifications often occur in late-onset disease & may wax & wane over time
- Calcifications are more commonly seen in alcoholic, hereditary, late-onset idiopathic & tropical pancreatitis

Abdominal Ultrasound (US)

- Findings consistent w/ chronic pancreatitis include the following:
  - Pancreatic duct dilation, presence of ductal stones, calcifications or pseudocysts
  - Changes in parenchymal echotexture & gland size
- Mild changes are less specific
- Overlying bowel gas may make adequate visualization of the pancreas difficult

Computed Tomography (CT) Scan

- Used as one of the 1st-line cross-sectional imaging tests aside from magnetic resonance imaging (MRI) to detect chronic pancreatitis since it is noninvasive & has relatively good sensitivity for diagnosing moderate-severe chronic pancreatitis
- Has a test sensitivity of 75-90% & specificity of at least 85%
- Pathognomonic findings include calcifications within the pancreatic ducts or parenchyma &/or dilated main pancreatic ducts together w/ parenchymal atrophy
- CT scanning is able to identify most complications of chronic pancreatitis & other abdominal pathologies that may present w/ signs & symptoms similar to those of chronic pancreatitis

2 DIAGNOSIS (CONT'D)

Imaging Exams of the Pancreas (Cont'd)

Endoscopic Retrograde Cholangiopancreatography (ERCP)

- Considered the "de facto" gold standard because it is currently the most specific & sensitive test of pancreatic structure
- Useful for patients in whom other tests are nondiagnostic or unavailable
- Diagnosis is based on abnormalities seen in the main pancreatic duct & its branches
- Pathognomonic findings consist of a markedly dilated pancreatic duct w/ alternating strictures ("chain-of-lakes" appearance)
- Advantage is therapy may also be administered eg pancreatic duct stenting or stone extraction; main disadvantage is that it is the riskiest exam for chronic pancreatitis
- Finer changes seen in early disease are often subject to inter-observer interpretation variability

Endoscopic US (EUS)

- A sensitive imaging modality for diagnosing chronic pancreatitis, specifically its early stages
- Due to its invasiveness & lack of specificity, EUS should only be used if the diagnosis is uncertain after performing a cross-sectional imaging
- Diagnosis is based on abnormalities in the pancreatic duct &/or parenchyma
- Eliminates imaging problems encountered w/ abdominal US eg overlying bowel gas
- May be used to obtain pancreatic tissue &/or secretions

Magnetic Resonance Imaging (MRI) w/ Magnetic Resonance Cholangiopancreatography (MRCP)

- Detailed images of the pancreas are seen similar to a CT scan
- Test is noninvasive & does not require sedation
- Secretin-enhanced MRCP may be performed in patients w/ high clinical suspicion but cross-sectional imaging or EUS is non-confirmatory
  - Can identify subtle abnormalities in the duct, eg an ectatic duct or dilated branches

Genetic Testing

- Identifies pancreatitis-related disorders (eg *CFTR* variants w/ a *CFTR*-related disorder or cystic fibrosis), aids in decision making & treatment choices, & helps prevent irreversible chronic pancreatitis
- Indicated in the following: Uncertain etiology, age <35 years old, family history of pancreatic diseases or disease persistence after treatment intervention
- At a minimum, *CFTR, CTRC, SPINK1,* & *PRSS1* gene mutation analysis should be evaluated in patients w/ idiopathic chronic pancreatitis

Pancreatic Histology

- Gold standard for diagnosis in high-risk patients when clinical evidence is strong for chronic pancreatitis but imaging tests are inconclusive
- Routine biopsy is risky & only rarely performed
- Changes may not be uniform throughout the gland so a single random tissue sampling may not be diagnostic

Identify Presence of Treatable Complications

- Pain is the most common symptom of chronic pancreatitis that will need medical care; therefore, the initial evaluation should also include the identification of conditions that are treatable
  - The biochemical & radiological findings of chronic pancreatitis do not correlate well w/ the intensity of patient's pain
- CT scan can be used to identify fluid collections, pseudocysts, mass lesions or pancreatic duct dilation; duodenal or bile duct obstruction may also be identified
- Barium radiography or ERCP may be necessary to define obstructions

3 ALTERNATIVE DIAGNOSIS

- Other conditions that need to be ruled out include peptic ulcer disease, biliary obstruction, pancreatic carcinoma, pseudocysts, pancreatic duct stricture or stone, fibrosis & inflammation of the pancreatic islet cells from chronic DM, age-related fibrosis or atrophy, autoimmune inflammation, immune system-altering medications (eg Cyclosporine), renal disease causing secondary pancreatic effects

A NON-PHARMACOLOGICAL THERAPY

Abstinence from Alcohol & Tobacco

- Patients should be encouraged to abstain from drinking alcohol & smoking
- Mortality has been found to increase w/ continued smoking & abuse of alcohol
  - Alcohol abuse speeds up the development of pancreatic dysfunction
  - Smoking accelerates disease progression & may increase pancreatic cancer risk
- Diminishing alcohol intake has been seen to result in decreased pain associated w/ chronic pancreatitis

Diet

- Adequate hydration is helpful
- Malnourished patients should consume 5-6 meals/day of high-energy, high-protein food
- Dietary fat need not be restricted unless steatorrhea is uncontrolled
- Oral nutritional supplements w/ medium chain triglycerides (MCTs) can be given to patients if adequate supplementation w/ enzymes does not improve malabsorption
  - MCTs improve pain by minimally increasing CCK levels or through its antioxidant effect
- Patients w/ malabsorption can be supplemented w/ water-soluble (thiamine, folic acid, vitamin B12) & fat-soluble (vitamins A, D, E, K) vitamins & minerals (eg iron, magnesium, selenium, zinc)
- As patients w/ chronic pancreatitis are at risk for osteoporosis, patients are advised to take adequate calcium & vitamin D, & if warranted, pancreatic enzyme supplementation

Nutrition

- Patients w/ malnutrition unresponsive to oral nutritional support should be given enteral nutrition
  - May be administered via a nasojejunal tube in patients w/ pain, persistent N/V, delayed gastric emptying & gastric outlet syndrome
  - Patients needing enteral nutrition should be supplemented w/ pancreatic enzymes if signs of exocrine failure are present
- Parenteral nutrition, preferably via a central venous access, may be given to patients intolerant of enteral nutrition or in those w/ gastric outlet obstruction or complex fistulating disease

B PHARMACOLOGICAL THERAPY

- Patient's symptoms should be regularly assessed so that failure of any treatment intervention may be quickly identified & timely institution of invasive measures can be done in order to prevent unnecessary progression of the disease & development of complex pain syndromes

Analgesics

- Pain relief is a primary priority in the management of disease
- Goal of treatment is control of pain to a satisfactory or tolerable level rather than total elimination of pain
- Considered if pain was unresponsive to pancreatic enzyme supplementation
- Non-narcotic agents may be tried initially; however, most patients need more potent agents for pain relief eg narcotics/opiates
  - Consider giving opiates to patients w/ painful chronic pancreatitis only when all other therapeutic options have failed
- Pregabalin or Gabapentin may be considered as adjuvant therapy if pain is unresponsive to narcotics
- Pain medication should not be withheld even if there is concern regarding possible addiction

Pancreatic Enzyme Supplements

- Initiated in patients w/ diagnosed pancreatic exocrine insufficiency
- Goal is to give at least 10% of normal pancreatic output w/ every meal
- Non-enteric-coated preparations are preferred for the treatment of pain while enteric-coated preparations are used more frequently for the treatment of exocrine insufficiency
- **Action:** Negative feedback inhibition of the pancreas
  - Administered enzymes denature CCK-releasing peptide which results in reduced CCK release
  - CCK release is thought to increase pancreatic pain
- Because neural control also plays a role in controlling pancreatic secretion, suppression of secretion through this method is not complete & may be variable
- It has been shown that pancreatic enzyme replacement provided pain relief when given early in the course of the disease & may be indicated prior to the onset of clinically detectable exocrine insufficiency
  - Some studies have shown that response is generally poor in patients w/ advanced chronic disease or w/ significant abnormalities of the pancreatic duct ("big-duct" disease)
- A trial of treatment may be beneficial for patients w/ less advanced disease who have failed more simple medical measures
- Concomitant treatment w/ gastric acid-suppressing agents is recommended to avoid inactivation of non-enteric-coated pancreatic enzymes by gastric acid
- Efficacy of supplementation may be assessed w/ improvement of patient's gastrointestinal symptoms & nutritional status

B PHARMACOLOGICAL THERAPY (CONT'D)

Inhibitors of Gastric Acid Secretion

- **Action:** Inhibition of acid secretion leads to a higher duodenal pH, which may in turn reduce pancreatic secretion & pain
- Histamine$_2$-receptor antagonists (H_2RAs) & proton pump inhibitors (PPIs) may be used
- There is no definite evidence showing the effectiveness of this therapy, but it is commonly tried due to its safety & ease of administration
- Concomitant acid suppression is also recommended during therapy w/ non-enteric-coated pancreatic enzymes to prevent enzyme inactivation by gastric acid
- If increase in pancreatic enzyme dose or addition of a PPI fails to improve patient's clinical response, consider excluding other causes of malabsorption, eg small intestinal bacterial overgrowth

Adjunctive Therapy

Antidepressants

- Depression may lower the pain threshold of some patients
- Pain may also have important psychiatric, psychosocial & psychosomatic components
- Antidepressants, eg selective serotonin reuptake inhibitors or tricyclic antidepressants, may be used as adjunctive therapy to alleviate depression & to potentiate the effect of narcotics

Antioxidants

- May be considered in the treatment of pain in patients w/ early chronic pancreatitis
- Antioxidants used in clinical trials include ascorbic acid, beta-carotene, methionine & selenium
- Studies have not yet determined optimal type of antioxidants & dosage for treatment

C ENDOSCOPIC THERAPY

- Goal of treatment is to improve pancreatic duct drainage by relieving obstruction that may be caused by ampullary stenosis, stones or strictures
- Pancreatic duct decompression achieves lower ductal pressures which may then result in reduced pain
- A trial of therapy is usually indicated in patients whose pain cannot be adequately controlled by medical therapy ie analgesics, narcotics
- Patients who are most likely to benefit are those who have advanced structural defects of the pancreatic duct
- Specific endoscopic therapies include stent placement, stone removal, stricture dilation, & duct sphincterotomy
- Endoscopic ultrasound-guided celiac plexus block or neurolysis can also decrease pain for weeks to months, may decrease or eliminate the need for oral analgesia, & can be repeated as needed

D SURGERY

- Early surgical intervention may more effectively relieve pain, decrease the need for re-intervention & improve pancreatic function preservation
- Surgery may be considered in the following groups of patients:
  - W/ persistent pain unresponsive to medical therapy
  - Patients whose pancreatic ductal anatomy is not suitable for endoscopic treatment
  - Patients in whom endoscopic therapy has failed
    - Surgery is superior to endoscopy for control of pain in a dilated pancreatic duct
  - Presence of complications, eg infection or symptomatic compression of adjacent structures
  - As 1st-line treatment for suspected pancreatic cancer
- Procedures that may be performed are pseudocyst decompression, ductal decompression, pancreatic resection, denervation procedures, & total pancreatectomy
- The choice of procedure depends on the patient's predominant condition, though more preferred are the tissue-preserving procedures
  - Ductal dilatation is best treated w/ drainage & decompression procedures
  - "Small-duct" disease is usually treated w/ pancreatic resection
  - Pseudocysts >5 cm in size & persisting for >6 months should be drained
  - Refractory chronic pain in highly selected patients is treated w/ total pancreatectomy w/ islet autotransplant only when all other treatment measures are unsuccessful

E TREATMENT OF COMPLICATIONS

- Complications of chronic pancreatitis result from endocrine & exocrine insufficiency
- Other complications such as a pancreatic pseudocyst, gastroparesis due to chronic pancreatitis, duodenal or biliary obstruction, or a secondary pancreatic cancer should be identified & treated accordingly

Diabetes Mellitus

- Diabetes results from destruction of pancreatic acinar cells
  - Insulin secretion is not completely lost while glucagon secretion is reduced
- Treatment is often directed at controlling urinary glucose losses rather than blood sugar levels
  - Avoid tight control of glucose levels as treatment-induced hypoglycemia can be fatal especially in malnourished patients
- Insulin is usually required, but some patients may still respond to oral antidiabetic agents
- Monitor patients for complications of long-standing diabetes eg nephropathy, neuropathy & retinopathy

Maldigestion

- Enzyme supplementation w/ lipase during & after a meal may reduce steatorrhea
- Supplementation w/ fat-soluble vitamins is beneficial & MCTs can help prevent weight loss
- Screen patients for micronutrient & macronutrient deficiencies at least annually
- Periodically assess for malnutrition including tests for osteoporosis
- Response to treatment may be measured through loss of visible stool fat, improved stool consistency, weight gain & normalization of fat-soluble vitamin levels

Pancreatic Malignancy

- Although the prevalence of pancreatic ductal adenocarcinoma is high in patients w/ chronic pancreatitis, there is currently no definitive benefit in screening patients for pancreatic malignancy

Dosage Guidelines

DIGESTIVES		
Drug	**Dosage**	**Remarks**
Pancreatin[1] (Lipase, Amylase & Protease)	Individualized dosage according to the degree of maldigestion & fat content of the meal **Required dose range:** 25,000-80,000 lipase u/kg/meal, ½ of individual dose for snacks	**Adverse Reactions** • GI effects (N/V, abdominal discomfort, loose stools); hypersensitivity reactions (lacrimation, sneezing, rashes); mucosal irritation or stomatitis **Special Instructions** • Instruct patient to swallow capsules whole to avoid irritation of the oral mucosa • Maintain adequate hydration during treatment

[1]Various combination products are available. Please see the latest MIMS for specific formulations.

HISTAMINE$_2$-RECEPTOR ANTAGONISTS (H_2RAs)		
Drug	**Dosage**	**Remarks**
Cimetidine	800-1600 mg/day PO in 4 divided doses, taken 60-90 min before meals	**Adverse Reactions** • CNS effects (headache, dizziness, somnolence, insomnia, agitation); GI effects (diarrhea, N/V); Other effects (rashes, myalgia, arthralgia) • Altered LFTs, reversible confusion in the elderly & those w/ renal failure have occasionally occurred • Rarely reported effects: CV effects (tachycardia, bradycardia, hypotension); Hematologic effects (leukopenia, thrombocytopenia, agranulocytosis); Other effects (acute pancreatitis, hepatotoxicity, hypersensitivity reactions) • Cimetidine has weak anti-androgenic effects; impotence & gynecomastia have occurred & are usually reversible **Special Instructions** • IV injections should be given slowly; IV infusion is preferred (especially for high doses & in patients w/ CV impairment) • Use w/ caution in patients w/ hepatic & renal impairment; dose adjustment recommended • Cimetidine may reduce hepatic metabolism of some drugs through inhibition of cytochrome P450 isoenzymes; closely monitor those on oral anticoagulants, Lidocaine, Phenytoin or Theophylline; dose reduction may be necessary
Famotidine	20-40 mg PO 12 hrly **Patients unable to take PO med:** 20 mg IV 12 hrly	
Nizatidine	150-300 mg PO 12 hrly	
Ranitidine	150 mg PO 12 hrly **or** 300 mg PO at bedtime **Patients unable to take PO med:** 50 mg IM/IV 6-8 hrly	
Roxatidine	75 mg PO 12 hrly **or** 150 mg PO at bedtime	

All dosage recommendations are for non-pregnant & non-breastfeeding women, & non-elderly adults w/ normal renal & hepatic function unless otherwise stated.
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Dosage Guidelines

PROTON PUMP INHIBITORS (PPIs)		
Drug	**Dosage**	**Remarks**
Esomeprazole	20-40 mg PO 24 hrly	**Adverse Reactions** • Generally well tolerated; most commonly reported: Headache, diarrhea, rash • Less common: GI effects (constipation, flatulence, abdominal pain, N/V, dry mouth); Dermatologic effects (pruritus, urticaria); Musculoskeletal effects (arthralgia, myalgia); Hematologic effects (eosinophilia, leukopenia, thrombocytopenia); Other effects (dizziness, fatigue, insomnia, cough, upper resp tract infection) • Hypersensitivity reactions, elevated liver enzymes, & isolated cases of photosensitivity & hepatotoxicity have been reported **Special Instructions** • Use w/ caution in patients w/ hepatic impairment; dose adjustment recommended • Concomitant use w/ Atazanavir or Nelfinavir is not recommended (PPIs reduce exposure to these drugs) • Exclude possibility of gastric malignancy prior to treatment • Bone fracture: Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. Patients should use the lowest dose & shortest duration of PPI therapy appropriate to the condition being treated
Lansoprazole	15-30 mg PO 24 hrly	
Omeprazole	10-40 mg PO 24 hrly **Patients unable to take PO med:** 40 mg IV 24 hrly	
Pantoprazole	20-40 mg PO 24 hrly **Patients unable to take PO med:** 40 mg IV 24 hrly	
Rabeprazole (Na rabeprazole, Sodium rabeprazole)	10-20 mg PO 24 hrly	

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