

Chronic Pancreatitis

Clinical Features and Diagnosis

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Core Curriculum/Practice Guidelines

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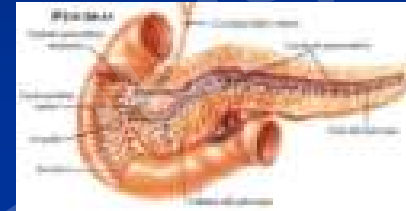
Chronic Pancreatitis

- General
- Pathophysiology
- Clinical Manifestations
- Diagnosis
- Complications
- Future Directions for treatment

Initial Thoughts:

Yahoo! Web Hits

- Acute pancreatitis 830K
- Chronic pancreatitis 915K
- Pancreatitis 2 million
- Pancreatic cancer 5.4 million
- Richard Wright 21.6 million



I can barely keep up with Dr. McClave's travels. How did my name become so popular?

Why bother?

Pancreas is widely tested on the
Boards!

General Info

- **Frequency: In the US:** Based on estimates from hospital discharge data in the United States, approximately 87,000 cases of pancreatitis occur annually.
- **Race:** Hospitalization rates for blacks are 3 times higher than for whites
- **Sex:** males are affected more commonly than females (6.7 versus 3.2 per 100,000 population).
 - Sex differences with respect to etiology also exist.
 - alcohol-induced illness is more prevalent in males,
 - idiopathic and hyperlipidemic-induced pancreatitis is more prevalent in females
 - equal sex ratios are observed in chronic pancreatitis associated with hereditary pancreatitis.
- **Age:** In aggregate, the mean age at diagnosis is 46 years, plus or minus 13 years.

Pathogenesis

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Pathophysiology

- Alcohol is the dominant etiologic factor and the most widely studied.
- A linear relationship exists between the amount of alcohol ingested and the risk of developing chronic pancreatitis.
- Fewer than 10% of people with alcoholism actually develop the disease.
- “Pancreatic cirrhosis???”

Alcoholic Pancreatitis Theories

■ Abnormal secretion

- Secretory defects favor the formation of calcium-protein complexes that lead to intraductal protein precipitates that obstruct ductules

■ Necrosis Fibrosis

- Etoh has specific cytotoxic effects on acinar cells that act independently to cause tissue damage, necrosis, and ultimately fibrosis.

Introduction

- CP is an inflammatory condition that results in
 - Permanent structural changes in the pancreas which lead to:
 - Abdominal Pain
 - Pancreatic insufficiency

Etiologies

- Etoh
- Idiopathic (10-20%)
- Tropical/nutritional
- Inherited (CF)
- Traumatic
- Autoimmune
- Metabolic
 - Hypertriglyceridemia
 - Hypercalcemia
- OBSTRUCTIVE
 - Benign obstructive
 - SOD
 - Papillary stenosis
 - Pancreas divisum c
obstruction of accessory
ampulla
 - Neoplastic obstruction
 - Tumors of ampulla or
ductal system

Differential Diagnosis

- Carcinoma
- Autoimmune pancreatitis
- Lymphoma
- Pancreatic endocrine tumors
- A variety of other rare conditions.

Diagnosis

- The diagnosis of chronic pancreatitis can be challenging since laboratory studies and imaging procedures may be normal.
- WARNING!!! Patients may have symptoms suggestive of chronic pancreatitis but in fact have pancreatic carcinoma. *Think of this in someone without etoh history!!*

Diagnosis

- Clinical Symptoms
- Labs
- Imaging

Abdominal Pain



Abdominal Pain

- Abdominal pain is the cardinal feature of chronic pancreatitis.
- The pain is typically epigastric, often radiates to the back, is occasionally associated with nausea and vomiting, and may be relieved by sitting upright or leaning forward.
- The pain is often worse 15 to 30 minutes after eating.
- Early in the course of chronic pancreatitis, the pain may occur in discrete attacks; as the condition progresses, the pain tends to become more continuous.



Pain Patterns

- The pain pattern in chronic pancreatitis varies among patients.
- Prospective cohort of 207 patients with alcoholic chronic pancreatitis in which two typical pain patterns were observed [ref].
- The first was characterized by episodes of pain (usually lasting less than 10 days) with pain free intervals lasting from months to more than a year.
- The second pattern was characterized by prolonged periods of daily pain or clusters of severe pain exacerbations often requiring repeated hospitalizations.

Pain Patterns

- Although abdominal pain is the most consistent finding in patients with chronic pancreatitis, it may be absent in some cases.
- In one series, for example, 20 percent of patients with chronic pancreatitis presented with evidence of pancreatic exocrine or endocrine dysfunction in the absence of pain [ref 1].
- These findings are consistent with a second study in which 45 percent of asymptomatic alcoholics had evidence of chronic pancreatitis on postmortem examination [ref 2].

Layer, P, Yamamoto, H, Kalthoff, L, et al. The different courses of early- and late-onset idiopathic and alcoholic pancreatitis. *Gastroenterology* 1994; 107:1481.

Clark, E. Pancreatitis in acute and chronic alcoholism. *Am J Dig Dis* 1942; 9:428.

Lab Testing

Tests of Function



Lab Studies

- Serum concentrations of amylase and lipase may be slightly elevated in patients with chronic pancreatitis, but are more commonly normal for the following reasons:
 - Chronic pancreatitis is a patchy, focal disease, leading to a minimal increase in pancreatic enzymes within the blood.
 - There is frequently significant fibrosis, resulting in decreased concentrations of these enzymes within the pancreas.
 - *The absolute serum concentrations of amylase and lipase have no prognostic significance.*
- The complete blood count, electrolytes, and liver function tests are typically normal.

Pancreatic Insufficiency



Pancreatic Insufficiency

- Patients with severe pancreatic exocrine dysfunction cannot properly digest complex foods or absorb digestive breakdown products.
- Nevertheless, clinically significant protein and fat deficiencies do not occur until over 90 percent of pancreatic function is lost [ref].

DiMagno, EP, Go, VL, Summerskill, WH. Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. N Engl J Med 1973; 288:813.

Pancreatic Function Tests

- Multiple functional tests to assess the pancreas have been examined.
- The gold standard is the secretin stimulation test.

Pancreatic Function Tests

Pancreatic Function Tests[†]

	Sensitivity (percent)	Specificity (percent)
Tubeless tests		
Fecal chymotrypsin	78	94
Trypsin radioimmunoassay	33	65
Serum pancreatic polypeptide	48 to 76	86 to 93
Dual-label Schilling	Not reported	Not reported
Quantitative stool fat	Not reported	Not reported
Duodenal-intubation tests		
Secretin-pancreozymin	75 to 90	80 to 90
Lundh	66 to 94	Not reported

[†]Adapted from Steer, ML, Waxman, I, Freedman, SD, N Engl J Med 1995; 332:1482.

Secretin Stimulation Test

- The basis for this test is that secretin causes the secretion of bicarbonate-rich fluid from the pancreas.
- A dual lumen catheter (Dreiling tube) is placed into the duodenum usually by endoscopic placement over a guide wire, allowing sampling of the duodenal contents.
- Intravenous secretin (0.2 mcg/kg) is administered, followed by collection of duodenal juice.
- A peak bicarbonate concentration of less than 80 meq/L is consistent with chronic pancreatitis.
- The secretin test may be normal in isolated pancreatic insufficiency without chronic pancreatitis.

Fat Malabsorption

- **Fat malabsorption** — Steatorrhea usually occurs prior to protein deficiencies since lipolytic activity decreases faster than proteolysis [ref].
- The clinical manifestations of fat malabsorption include loose, greasy, foul smelling stools that are difficult to flush.
- Malabsorption of the fat soluble vitamins (A, D, E, K) and vitamin B12 may also occur, although clinically symptomatic vitamin deficiency is rare [ref].

Mergener, K, Baillie, J. Chronic pancreatitis. Lancet 1997; 350:1379

Toskes, PP, Hansell, J, Cerda, J, Deren, JJ. Vitamin B 12 malabsorption in chronic pancreatic insufficiency. N Engl J Med 1971; 284:627.

Steatorrhea

- Steatorrhea can be diagnosed qualitatively by Sudan staining of feces, or quantitatively by determination of fecal fat excretion per 24 hours on a 100 g fat diet (still the gold standard to diagnose steatorrhea).
- The quantitative test is usually performed over 72 hours; *excretion of more than 7 g of fat per day is diagnostic of malabsorption*, although patients with steatorrhea often have values greater than 20 g/day.
- In the proper clinical setting (eg, in a patient with typical symptoms of abdominal pain), confirmation of increased fecal fat excretion may be sufficient to diagnose chronic pancreatitis.

Fecal Elastase

- Measurement of fecal elastase can be helpful for evaluating pancreatic exocrine dysfunction.
- A protein found in both pancreatic secretion and feces
- Among pancreatic function tests, *fecal elastase measurement is the most sensitive and specific, especially in the early phases of pancreatic insufficiency.*
- In addition, its values are independent of pancreatic enzyme replacement therapy and require only a single random stool sample.
- According to unpublished data from the manufacturer, values less than 200 ug/g are suggestive of pancreatic insufficiency (sensitivity and specificity of 93 percent).

Pancreatic Diabetes

- Glucose intolerance occurs with some frequency in chronic pancreatitis, but overt diabetes mellitus usually occurs late in the course of disease.
- Patients with chronic calcifying disease may develop diabetes more frequently than those with chronic noncalcifying disease [ref].
- Up to 70% of CP will develop diabetes
- **“Brittle diabetes”** because CP destroys insulin-producing beta cells and glucagon-producing alpha cells (frequent hypoglycemia)

Del Prato, S, Tiengo, A. Pancreatic diabetes. Diabetes Reviews 1993; 1:260.

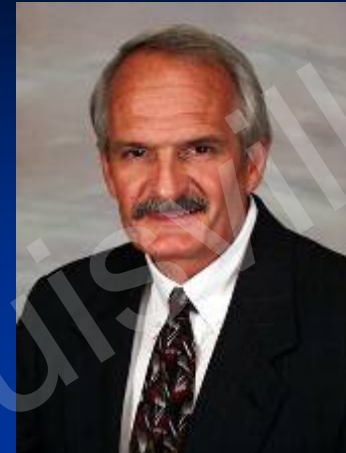
Imaging

Tests of Structure

Imaging

- X-ray (30%)
- US (sn 65% sp 85%)
- CT (sn 85% sp 85%)
- EUS
- MRCP
- ERCP
- Secretin MRCP

Guess Which One I like?



Sam is sneaky!!!!!!!!!!!!



Have I seen her on
TV somewhere?

Plain Films

- Calcifications within the pancreatic duct are present on plain film in 30 percent of patients with chronic pancreatitis.
- Calcium deposition is most common with alcoholic pancreatitis, but is also seen in the hereditary and tropical forms of the disorder; it is rare in idiopathic pancreatitis

Plain Film



30% calcifications

Pancreatic calcifications Plain film of the abdomen shows pancreatic calcifications (arrows) in a patient with chronic pancreatitis. (With permission from Steer, ML, Waxman, I, Freedman, SD, N Engl J Med 1995; 332:1482.)

CT, MRI & US

- Transabdominal ultrasonography (US), CT scan, and MRI may show calcifications, ductal dilatation, enlargement of the pancreas, and fluid collections (eg, pseudocysts) adjacent to the gland.

CT



Acute pancreatitis superimposed upon chronic pancreatitis CT scan through the upper abdomen in a patient with chronic pancreatitis demonstrates a large complex inflammatory mass in the head of the pancreas (arrow) with calcifications (indicative of chronic disease) and low attenuation areas of necrosis. Courtesy of Jonathan Kruskal, MD.

CT



Chronic pancreatitis CT scan of a patient with chronic pancreatitis demonstrates coarse calcifications (arrow) distributed throughout the body and tail of the pancreas. Courtesy of Jonathan Kruskal, MD.

EUS

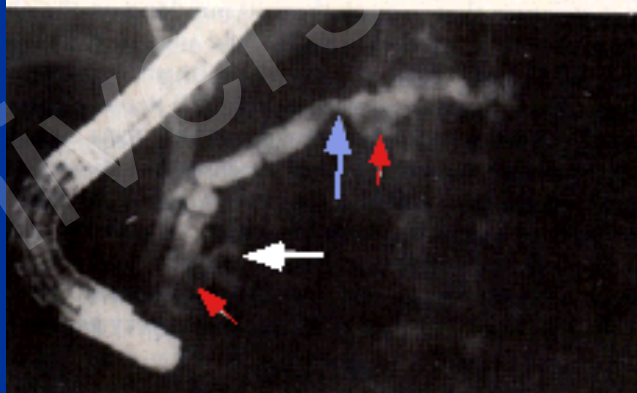
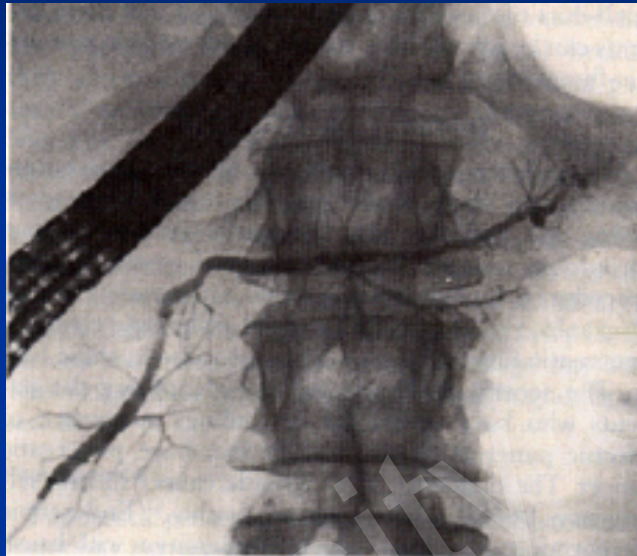
- Endoscopic ultrasonography (EUS) may be as sensitive as ERCP or pancreatic function testing, but requires a highly skilled gastroenterologist [ref].
- The most predictive endosonographic feature is the presence of stones.
- Other suggestive features include: visible side branches, cysts, lobularity, an irregular main pancreatic duct, hyperechoic foci and strands, dilation of the main pancreatic duct, and hyperechoic margins of the main pancreatic duct.
- Many endosonographers consider the presence of four or more of these features to be highly suggestive of chronic pancreatitis

Wallace, MB, Hawes, RH, Durkalski, VV, et al. The reliability of EUS for the diagnosis of chronic pancreatitis: Interobserver agreement among experienced endosonographers. *Gastrointest Endosc* 2001; 53:294.

ERCP

- ERCP is frequently the test of choice for the diagnosis of chronic pancreatitis when calcifications are not present on a plain film of the abdomen and there is no evidence of steatorrhea.
- Characteristic beading of the main pancreatic duct and ectatic side branches is diagnostic of chronic pancreatitis

ERCP



ERCP in chronic pancreatitis

Top panel: Normal subtraction endoscopic retrograde pancreatogram shows the filling of normal side branches and a smooth, nondilated main ductal system. Bottom panel: Endoscopic retrograde pancreatogram in a patient with chronic pancreatitis, revealing a dilated, tortuous main duct that contains stones or protein plugs (lucencies in duct marked by short red arrows). A stricture is visible in the midportion of the duct (blue arrow) and there is dilation of the uncinus-process branch (white arrow). (With permission from Steer, ML, Waxman, I, Freedman, SD, N Engl J Med 1995; 332:1482.)

MRCP

- A role for magnetic resonance cholangiopancreatography (MRCP) is emerging in the diagnosis of chronic pancreatitis.
- At present, MRCP does not have the sensitivity and specificity of ERCP, and therefore does not have a central role in assessing the pancreatic duct.
- A possible exception may be in patients who have gastric outlet or duodenal stenosis, or who have had surgical rearrangement (eg, Billroth II) or ductal disruption, resulting in ducts which cannot be assessed by ERCP.
- Secretin-enhanced MRCP is being increasingly studied for evaluation of pancreatic exocrine function and in the early diagnosis of chronic pancreatitis.
- The available data suggest that it may enhance visualization of the pancreatic duct, but whether it aids in the diagnosis of chronic pancreatitis remains to be determined.

Imaging vs. Lab

- Up to 15 percent of patients with an abnormal pancreatogram on ERCP have a normal secretin study or vice versa. Thus, these two tests should be viewed as complementary.

Complications (Hi-Yield)

- Pseudocysts
- Bile duct or duodenal obstruction
- Splenic vein thrombosis (gastric varices & GIB)
- Pseudoaneurysms
- Pancreatic cancer
- Pancreatic fistulas (tx c octreotide)
- Fat soluble deficiencies (KADE)- B12 defic 40%
- Pancreatic ascites (amylase > 1000)

Recent Articles

Cigarette smoking accelerates progression of alcoholic CP

- Retrospective Cohort of 934 subjects
- Compared smokers vs. nonsmokers and adjusted for ag, sex, center, etoh consumption
- Smokers diagnosed 4.7 years earlier ($p=.001$)
- Calcifications hazard ratio 4.7
- Diabetes hazard ratio 2.3

Autoimmune CP: unveiling a hidden entity

- After etoh cp, idiopathic cp is the most common cause of calcifying pancreatitis
- Retrospective case series revealed 6 cases of lymphoplasmacytic sclerosing pancreatitis
- Conclusion: lymphoplasmacytic sclerosing pancreatitis is an increasingly recognized cause of CP and should be considered in the eval of patients with CP and no discernible cause

Future Directions

Possible Treatments

Fibrosis is a dynamic and potentially reversible condition

- Increases in many “fibrogenic” cytokines correlate with the severity of episodes of acute pancreatitis

Gukovskaya AS et al/ Ethanol differentially regulates NF-kappaB activation in pancreatic acinar cells through calcium and protein kinase C pathways. Am J Physiol Gastrointest Liver Physiol 2004; 286:G204-G213.

Final Thought

Vitamin A as a Treatment of CP

“Professor Cave’s synopsis”



Dr. Cave's cytokine reduction program

CONCLUSIONS

- Clinical Symptoms
- Labs (fecal elastase is very promising)
- Imaging
- Pain relief is well beyond the scope of this talk!!

Questions?

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