Acute Pancreatitis

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Disclosures

- **No financial disclosures**

Objectives

1. Provide an overview of the diagnosis acute pancreatitis (AP)
2. Discuss the management of AP
3. Discuss important consensus recommendations

Epidemiology

- Acute pancreatitis (AP) is the leading cause of GI admission; 250,000 per year
- Annual cost is ~ $3 billion per year
- Incidence increases with age
- No gender predilection

Yadav. Gastroenterology 2013;144:1252.

Diagnosis of acute pancreatitis

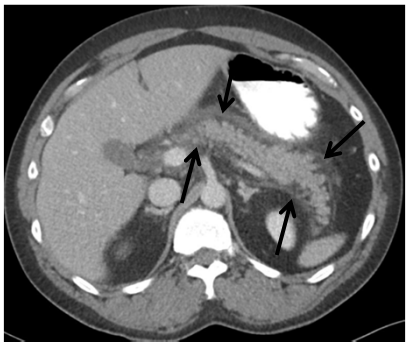
Diagnosis

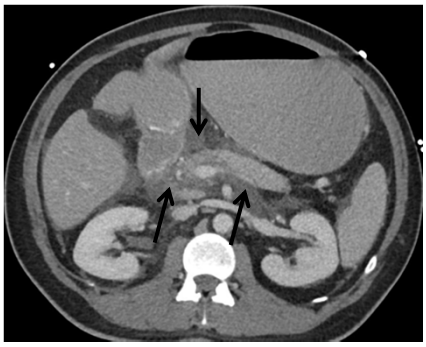
- **Two of the following are required:**

1. **Typical upper abdominal pain**
2. **Elevated lipase or amylase (>3x ULN)**
3. **Consistent radiographic features on cross-sectional imaging**

Tenner S. ACG guidelines: management of acute pancreatitis. Am J Gastroenterol 2013;108:1400.

Interstitial acute pancreatitis





Pitfall: Overuse of CT scanning in mild AP

- 60-70% of patients with diagnostically elevated pancreatic enzymes undergo CT within 48 hours
  - Necrosis or sequelae observed in <10%
- ACG: Indications for imaging with contrast:
  - Unclear diagnosis
  - Failure to improve within 48-72 hrs after admission

Dachs. Emerg Radiol 2015;22:239
Shinagare. Abdom Imaging 2015;40:272.
Tenner S. Am J Gastroenterol 2013;108:1400.

Etiologies of acute pancreatitis

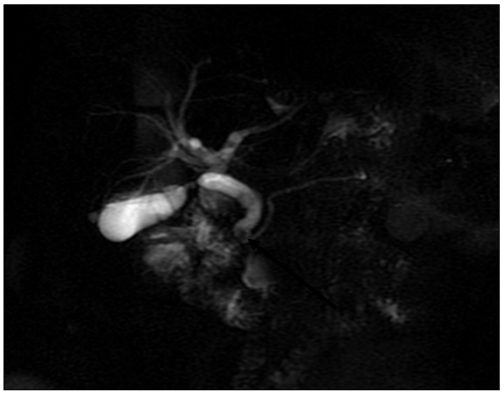
- Ampullary obstruction – gallstones, sludge, cancer, ampullary stenosis, parasites, (SOD)
- Toxins – EtOH
- Idiopathic
- Metabolic – hypertriglyceridemia, ↑ calcium
- Traumatic – post-ERCP, blunt trauma
- Congenital – choledochocele, annular pancreas, (pancreas divisum)
- Genetic – PRSS1, (CFTR)
- Misc. – medications, infections, vascular

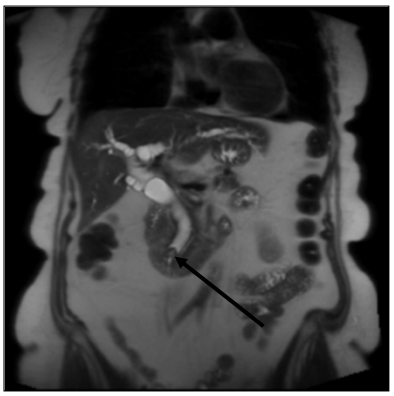
Biliary pancreatitis

- ACG: US should be performed in all patients with acute pancreatitis
  - Stones → cholecystectomy
  - Sludge → consider cholecystectomy
- The sensitivity for detection of a distal common bile duct stone with transabdominal US is low
- Elevated ALT >150 U/L; 95% PPV for gallstone pancreatitis

Tenner. Am J Gastroenterol 2013;108:1400
Tenner. Am J Gastroenterol 1994;89:1863

Choledocholithiasis on MRI/MRCP





Hypertriglyceridemia

- Explains up to 4% of acute pancreatitis
- Consider if TG level >1,000
- Diagnostic clues – lipemic serum, pseudohyponatremia, normal amylase
- Causes – severe hyperglycemia/uncontrolled DM, familial, alcohol, medications

Tsuang. Am J Gastroenterol 2009;104:984.

Drug-induced acute pancreatitis

Summary of Drug-Induced Acute Pancreatitis Based on Drug Class

Class Ia
α-methyldopa
Azodisalicylate
Bezafibrate
Cannabis
Carbimazole
Codeine
Cytosine Arabinoside
Dapsone
Enalapril
Furosemide
Isoniazid
Mesalamine
Metronidazole
Pentamidine
Pravastatin
Procainamide
Pyritonol
Simvastatin
Stibogluconate
Sulfamethoxazole
Sulindac
Tetracycline
Valproic acid

Class Ib
All-trans-retinoic acid
Amiodarone
Azathioprine
Clomiphene
Dexamethasone
Ifosfamide
Lamivudine
Losartan
Lynesterol/methoxyethinylestradiol
6- MP
Meglumine
Methimazole
Nelfinavir
Norethindronate/mestranol
Omeprazole
Premarin
Sulfamethazole
Trimethoprimsulfamethazole

Class II
Acetaminophen
Chlorthiazide
Clozapine
DDI
Erythromycin
Estrogen
L-asparaginase
Pegasparagase
Propofol
Tamoxifen

Class III
Aledronate
Atorvostatin
Carbamazepine
Captopril
Ceftriaxone
Chlorothalidone
Cimetidine
Clarithromycin
Cyclosporin
Gold
Hydrochlorothiazide
Indomethacin
Interferon/ribavirin
Irbesartan
Isotretinoin
Ketorolac
Lisinopril
Metalozone
Metformin
Minocycline
Mirtazapine
Naproxen
Paclitaxel
Prednisone
Prednisolone

Badalov. Clin Gastro Hepatol 2007;5:648-661

Drug-induced acute pancreatitis

Summary of Drug-Induced Acute Pancreatitis Based on Drug Class

Class IV
Adrenocorticotrophic hormone
Ampicillin
Bendroflumethiazide
Benzapril
Betamethazone
Capecytabine
Cisplatin
Colchicine
Cyclophosphamide
Cyproheptidine
Danazol
Diazoxide
Diclofenac
Difenoxylate
Doxorubicin
Ethacrinic acid
Famciclovir
Finasteride
5-fluorouracil
Fluvastatin
Gemfibrozil
Interleukin-2
Ketoprofen
Lovastatin
Mefanamic acid
Nitrofurantoin
Octreotide
Oxyphenbutazone
Penicillin
Phenophthalein
Propoxyphene
Ramipril
Ranitidine
Rifampin
Risperidone
Ritonovir
Roxithromycin
Rosuvostatin
Sertaline
Strychnine
Tacrolimus
Vigabatin/lamotrigine
Vincristine

Badalov. Clin Gastro Hepatol 2007;5:648-661

Other risk factors

- Cigarette smoking
- Non-white race
- Obesity
- Diabetes mellitus
  - ? Increased risk of acute pancreatitis secondary to incretin-based therapies:
    - GLP-1 analogues (-tide)
    - DPP-4 inhibitors (-gliptin)

Giorda. Endocrine 2015;48:461.
Sadr-Azodi. Gut 2012;61:262.

Management of acute pancreatitis

Risk stratification and classification

- Ranson's criteria
- APACHE
- BUN
- Hct
- C-reactive protein
- BISAP
- Revised Atlanta

<u>Predictors of severity:</u>

- Advanced age
- Obesity
- SIRS
- Organ failure

<u>Favorable prognosis</u>:

- HAPS

BISAP, bedside index of severity in acute pancreatitis
HAPS, harmless acute pancreatitis score

Revised Atlanta Criteria

	Organ failure	Local complications*	Morbidity	Mortality
Mild AP	No	No	↓	↓
Moderately-severe AP	No or transient (<48h)	Yes	↑	↓
Severe AP	Persistent	Yes	↑	↑

*Local complication - pancreatic/extra-pancreatic necrosis

Banks. Gut 2013;62:102.

Indications for transfer

- **Patients with AP treated at high-volume centers (>117 admission/yr) have a 25% lower RR of death**
- **<u>Reasons to consider transfer to a high-volume center</u>:**
  - **Lack of response to initial resuscitation**
  - **Persistent organ failure**
  - **Necrotizing pancreatitis with or without peri-pancreatic fluid collections**
  - **Unable to perform a clinically indicated ERCP**

Wu. Gastroenterology 2013;144:1272.
Singla. Gastroenterology 2009;137:1995.

Clinical management of AP

1. **IV fluids**
2. **Analgesia (no human studies)**
3. **Nutrition support**
4. **ERCP**
5. **Local complications**
6. **Systemic complications**

Wu. Gastroenterology 2013;144:1272.

IV fluid resuscitation

- ACG: Aggressive hydration (250-500 mL/hr) of isotonic crystalloid solution should be provided to all patients; unless CV or renal contraindications.
- ACG: Lactated Ringer's may be the preferred IV fluid
- Targets:
  - Decrease in hematocrit
  - Decrease in BUN
  - Maintenance of a normal creatinine

Tenner S. Am J Gastroenterol. 2013;108:1400.
Wu BU…Conwell DL. Clin Gastroenterol Hepatol. 2011;9:710.

Pitfall: Inadequate IV fluid resuscitation

- Early, aggressive fluid resuscitation is associated with decreased risk of:
  - Persistent SIRS (at 72 h)
  - Developing necrosis
  - Persistent organ failure (at 72 h)
  - Death
- Early = 6-12 h from presentation
- Must begin in the Emergency Department, including assessment of the response to volume challenge

Wall. Pancreas 2011:40:547.
Warndorf. Clin Gastroenterol Hepatol 2011;9:705.
Gardner. Pancreatol 2009;9:770.

Nutrition support

- An oral diet can be restarted early (24-48 hours) in most patients with mild AP
- Persistent or fluctuating levels of serum amylase or lipase are NOT contraindications to advancing diet
- In severe AP (or those unable to tolerate an oral diet) enteral nutrition (NG vs. NJ) is preferred over TPN
  - Enteral nutrition is associated with ↓ mortality, infections, and organ failure

Al-Omran. Cochrane Database Syst Rev 2010:CD002837.

Role of ERCP in management of AP

- Useful for management of gallstone pancreatitis:

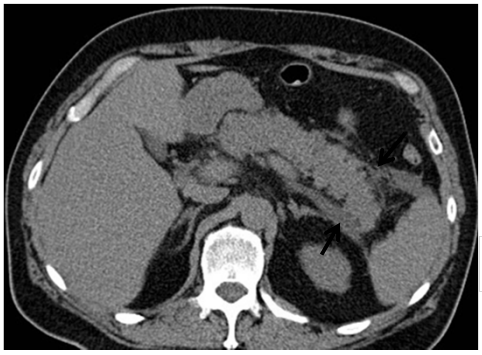
1. With cholangitis (emergent)
2. Retained CBD stone, pre/post-cholecystectomy (urgent)
3. Non-surgical candidate for cholecystectomy (non-urgent)

Local complications (necrotizing pancreatitis)

- ACG: Prophylactic antibiotics are NOT recommended for patients with sterile necrosis
- Not all patients with walled off pancreatic necrosis (WOPN) require intervention
- Approach to symptomatic (or infected) WOPN:
  - Delay (>4 weeks)
  - Drain
  - Debridement

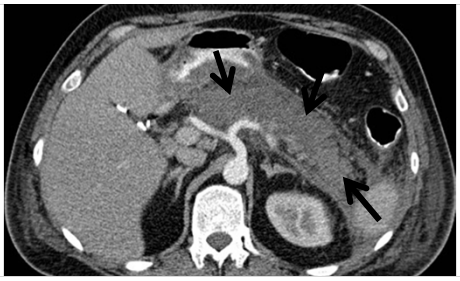
Tenner S. Am J Gastroenterol 2013;108:1400.
Freeman. Pancreas 2012;362:1491.
Villatoro. Cochrane Database Syst Rev 2010:CD002941.
Van Santvoort. N Engl J Med 2010;362;1491.

Evolution of walled off pancreatic necrosis

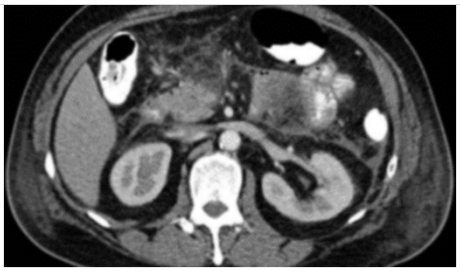


CT w/o contrast at presentation

1 week after presentation



1 week after presentation



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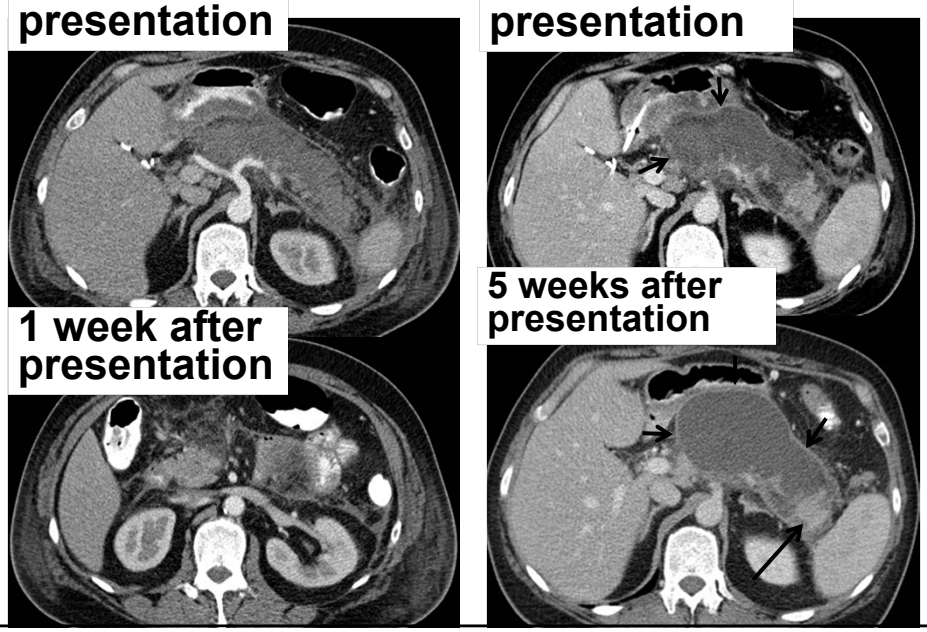
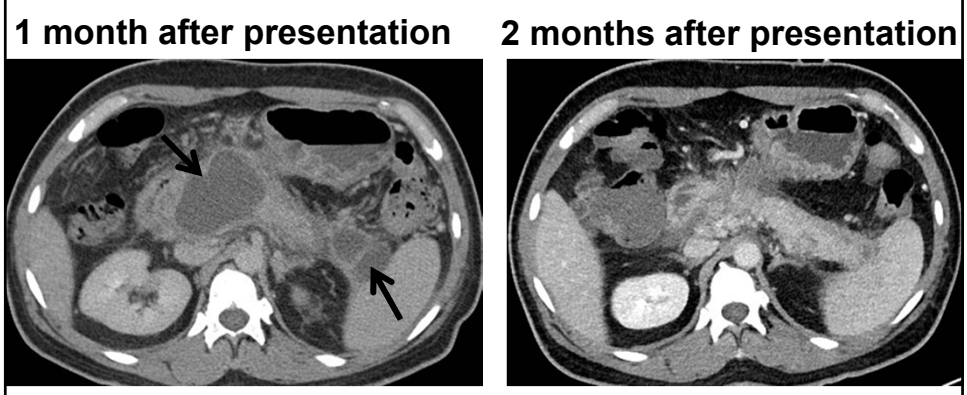
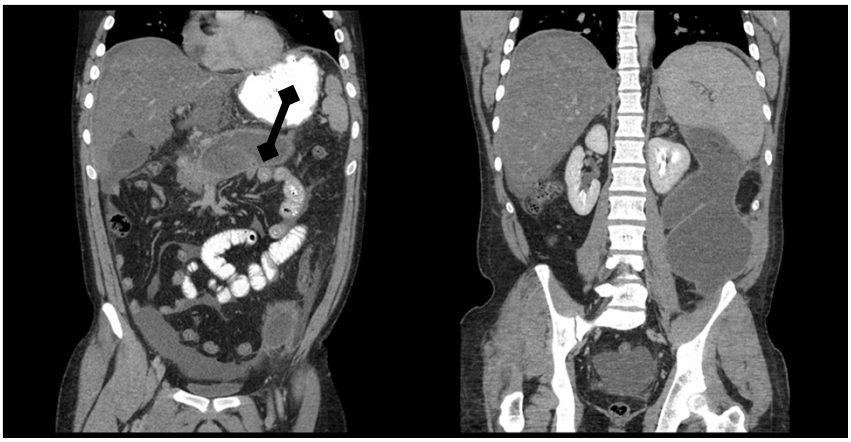


Delay interventions, if clinically possible



Debridement (endoscopic)



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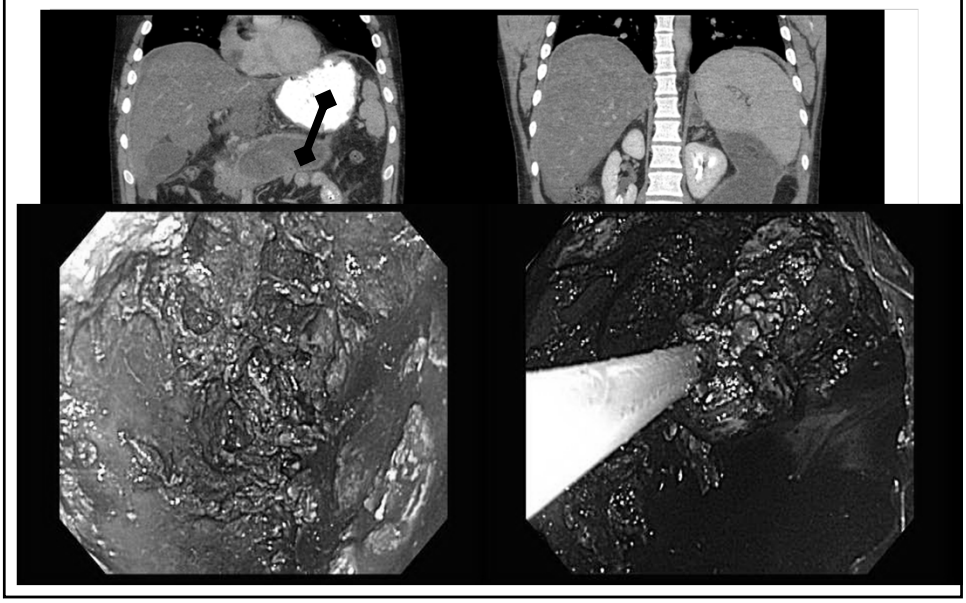

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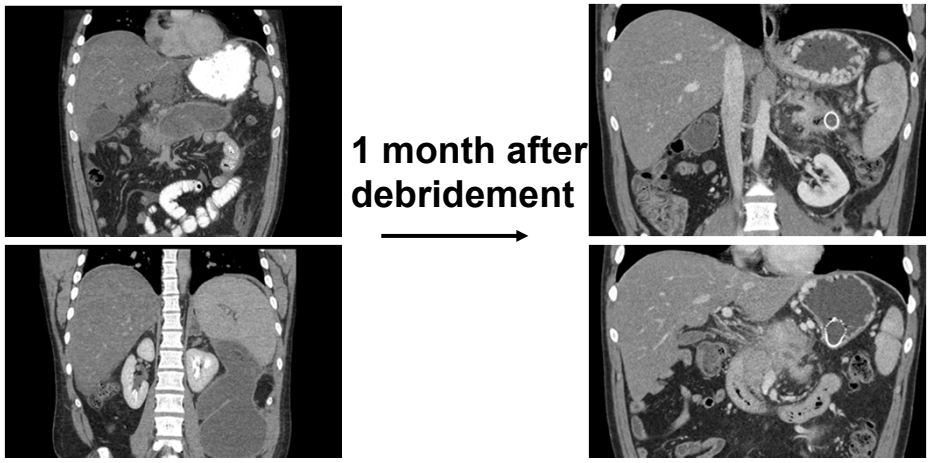

Discharge planning

- Plans for cholecystectomy for gallstone pancreatitis:
  - Mild severity – prior to hospital discharge
  - Severe – established surgery follow-up plans
- Risk factor modification – alcohol and tobacco
- Hypertriglyceridemia – stable glycemic regimen and Endocrinology follow-up
- Idiopathic – arrangements for additional outpatient evaluation

Wu, Conwell. Clin Gastro Hepatol 2010;8:417.

Risk factors for early readmission

- 15-20% of patients are readmitted within 60 days
- Risk factors:
  - Tolerating less than a solid diet at discharge
  - Persistent symptoms at discharge
  - Alcohol etiology
  - Organ failure
  - Local complications

Vipperla. Clin Gastroenterol Hepatol 2014;12:1911.
Whitlock. Am J Gastroenterol 2010;105:2492

Summary

- Diagnosis of acute pancreatitis can typically be made without cross-sectional imaging
- Risk stratification is helpful to determine appropriate utilization of resources
- The most important step in management is early, aggressive IV hydration
- Necrotizing pancreatitis is associated with high morbidity and requires a multi-disciplinary approach

Recommended reading

- **Wu B. Clinical Management of Patients with Acute Pancreatitis. Gastroenterology 2013;144:1272.**
- **Tenner S. American College of Gastroenterology (ACG) guidelines: management of acute pancreatitis. Am J Gastroenterol 2013;108:1400.**
- **OSU patient-oriented symposium on AP: http://internalmedicine.osu.edu/digestivediseases/about-the-division/pancdisease/acutepancreatitis/index.cfm**

Chronic Pancreatitis

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Disclosures

- No financial disclosures

Objectives

1. Discuss epidemiology of CP
2. Provide an overview of the diagnosis chronic pancreatitis (CP)
3. Discuss the management of CP

Epidemiology

- The incidence of chronic pancreatitis (CP) is low; <10/100,000
- Predominantly affects the middle-aged
- Male predominance

Yadav. Gastroenterology 2013;144:1252.

Classification for CP etiology (TIGAR-O)

- Toxic
  - Alcohol use (>4-5 drinks/day); attributable risk 40%
  - Cigarette smoking; attributable risk 25%

Classification for CP etiology (TIGAR-O)

- Toxic
  - Alcohol use (>4-5 drinks/day); attributable risk 40%
  - Cigarette smoking; attributable risk 25%
- Idiopathic
- Genetic – PRSS1 ("hereditary"), CFTR, SPINK1
- Autoimmune
- Recurrent acute pancreatitis
- Obstructive – duct obstruction (tumors, post endoscopic/surgical interventions)

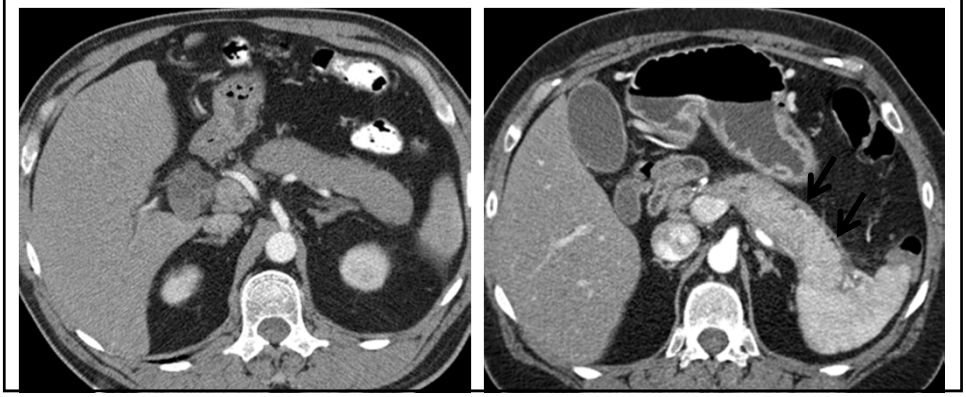
Hereditary pancreatitis

- Cationic trypsinogen gene (PRSS1)
  - Gain of function mutations → excessive trypsin activity
- Autosomal dominant with 80% penetrance
- Median onset is 10-20 years old
- Cumulative risk for pancreatic cancer is ~40%
  - Smoking: cancer develops earlier (50 vs. 70 yrs.)

Rebours. Am J Gastroenterol 2008;103:111.
Lowenfels. JAMA 2001;286:169.

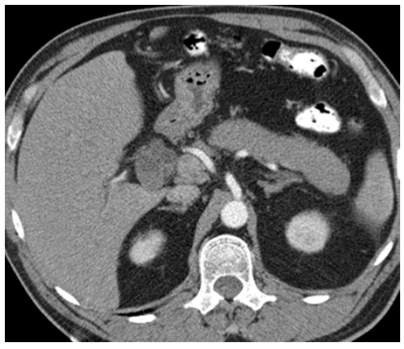
Autoimmune pancreatitis (type 1 AIP)

- Type 1 AIP has characteristic pathology, other organ involvement, and response to steroids
- Serum IgG4 levels are elevated in ~66% of patients
- Most have diffuse pancreatic enlargement ("sausage-shaped"), sometimes with a capsule sign

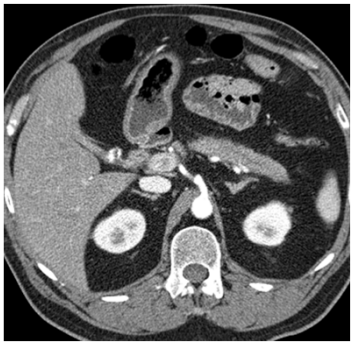


Autoimmune pancreatitis (type 1 AIP)

- ~100% response to steroid treatment
- Relapses occur in ~50% of patients with type 1 AIP



Presentation



One month after steroids

Hart. Gut 2013;62:1607.
Hart. Gut 2013;62:1771.

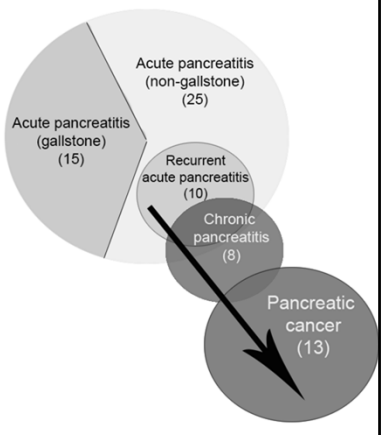
Autoimmune pancreatitis (type 1 AIP)

- ~100% response to steroid treatment
- Relapses occur in ~50% of patients with type 1 AIP
- Relapse treatment options:
  - Steroids alone
  - Steroids plus immunomodulator
  - Rituximab

Hart. Gut 2013;62:1607.
Hart. Gut 2013;62:1771.

Recurrent acute pancreatitis

- ≥2 episodes of AP with resolution of symptomatic and imaging abnormalities between episodes
- Occurs in ~20% of AP patients
- RAP is the strongest risk factor for progression to CP
  - HR of 4.57, 95% CI 3.40-6.14



Yadav. Gastroenterology 2013;144:1252.
Yadav. AJG 2012; 107:1096.
Lankisch. AJG 2009;104:2797.

Cigarette smoking and RAP

- Smoking is an independent, dose-dependent risk factor for developing RAP
  - HR 1.76, 95% CI 1.30-2.39
- Smoking increases the rapidity of progression to CP
- All patients with acute pancreatitis should be counselled re: smoking cessation

Yadav. Am J Gastroenterol 2012; 107:1096.
Yadav. Arch Int Med 2009;169:1035

Diagnosis of chronic pancreatitis

Diagnosis of CP

- An early, accurate diagnosis is important to provide an opportunity to interrupt disease progression
- However, diagnosis of early stage disease is challenging and less accurate than in advanced CP
- Considerations:
  - Clinical history – risk factors and symptoms
  - Pancreas morphology
  - Pancreas function

Conwell DL. Pancreas 2014;43:1143.

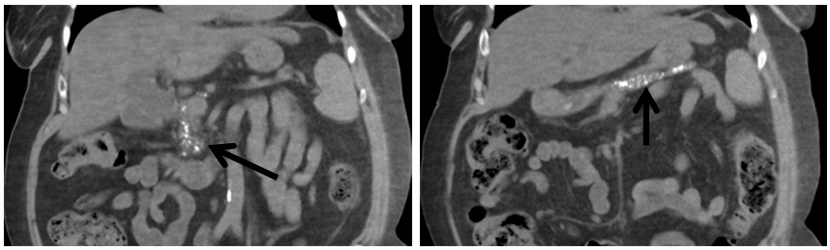
Diagnostic modalities

- CT imaging
- MRI/MRCP
- Endoscopic ultrasound (EUS)
- ERCP
- Pancreas function testing

Conwell DL. Pancreas 2014;43:1143.

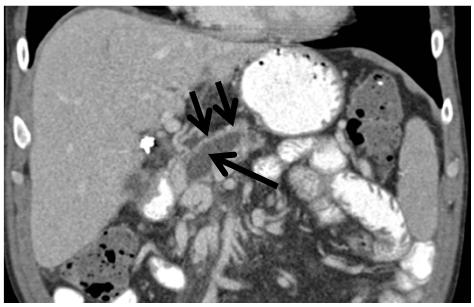
CT for diagnosis of CP

- **Helpful for identification of advanced CP**



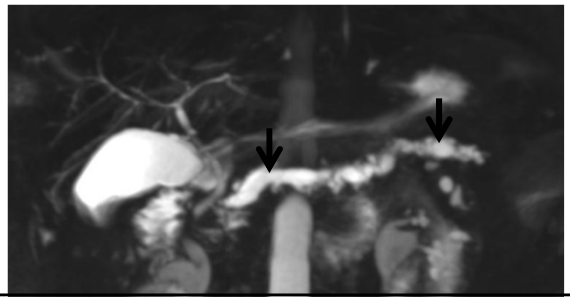
CT for diagnosis of CP

- **Helpful for identification of advanced CP**
- **Characteristic findings:**
  - **Calcifications**
  - **Ductal dilation**
  - **Atrophy**



MRI/MRCP for diagnosis of CP

- More sensitive for ductal changes than CT
- Findings:
  - Dilated pancreatic duct
  - Dilated side branches
  - Decreased T1 signal (suggests fibrosis)
  - Parenchymal atrophy
  - Poor visualization of calcifications



ERCP for diagnosis of CP

- No longer recommended for diagnosis of CP, due to availability of MRCP imaging

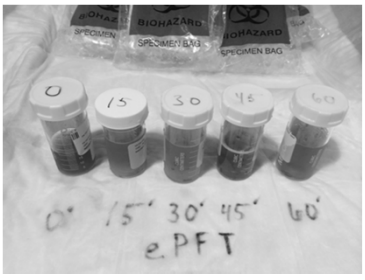
EUS for diagnosis of CP

- Often identifies non-specific, subtle abnormalities, so this should not be used in isolation
- <u>EUS criteria (need 5 or more)</u>:
  - Hyperechoic strands
  - Hyperechoic foci
  - Calcifications
  - Lobular contour
  - Cysts
  - Main pancreatic duct dilation
  - Irregular pancreatic duct margins
  - Hyperechoic pancreatic duct walls
  - Visible side branches

Stevens. Gastroinest Endosc Clin N Am 2013;23:735.

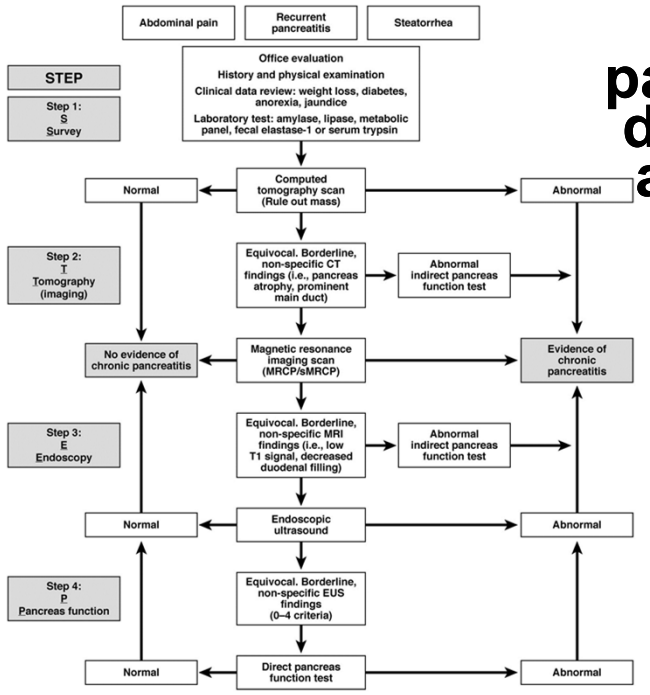
Pancreas function testing for dx of CP

- Direct PFTs: Pancreatic stimulation (secretin or CCK) → measure fluid output (bicarbonate concentration or lipase output)
- Primary value is to rule out chronic pancreatitis in those with chronic abdominal pain (NPV of 97%)
- Only available at a small number of academic centers



Ketwaroo. Am J Gastroenterol 2013;108:1360.
Conwell. Gastrointest Endosc 2003;57:37.

Chronic pancreatitis diagnostic algorithm



Conwell. Clin Gastroenterol Hepatol 2012;10:1088.

Management of CP

Screening/Management of complications

1. Pain
2. Endocrine insufficiency
3. Exocrine insufficiency
4. Metabolic bone disease
5. Pancreatic cancer

Pain management in CP

- Pain accounts for significant medical costs and poor social function and QOL
- Pain severity does not always correlate with the severity of underlying disease

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- Mechanisms for pain:
  - ductal obstruction
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Pain management in CP

- Pain accounts for significant medical costs and poor social function and QOL
- Pain severity does not always correlate with the severity of underlying disease
- Mechanisms for pain:
  - ductal obstruction
  - neural remodeling
- Management options:
  - Medical
  - Endoscopy
  - Surgery

Pain management: medical

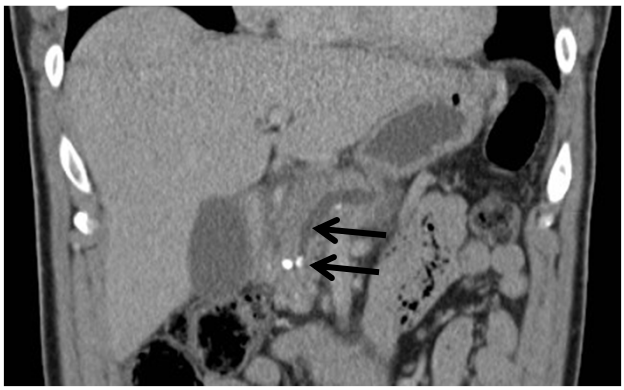
1. Alcohol abstinence - reduces pain (unpredictable)
2. Gabapentoids – pregabalin (up to 300 mg BID)
   - Decreased pain and opioid use vs. placebo
3. Antioxidants – mixed results; potentially reduces pain for some patients (young, idiopathic etiology)
4. Opioids – tramadol, then more potent opioids
5. Alternatives – TCA's, SSRI's, SNRI

- No convincing evidence for benefit: pancreatic enzymes and octreotide

Forsmark. Gastroenterology 2013;144:1282.

Pain management: endoscopy

- Goal: remove obstructions in the pancreatic duct
- Most beneficial for patients with small, pancreatic duct stones



Pain management: endoscopy

- Goal: remove obstructions in the pancreatic duct
- Most beneficial for patients with small, pancreatic duct stones
- EUS and ERCP interventions:
  - Biliary/pancreatic duct sphincterotomies
  - Pancreatic duct stent(s)
  - Stone extraction
  - Lithotripsy (intraductal vs. ESWL)
  - Celiac plexus block (controversial)

Pain management: surgery

- Goals:
  - Inability to exclude malignancy
  - Resection of diseased gland
  - Drainage of an obstructed pancreatic duct
- Several factors influence surgery selection:
  - Main pancreatic duct diameter
  - Diffuse vs. localized disease
  - Pre-operative diabetes status
  - Surgeon's expertise

Endoscopy vs. surgery for pain relief from CP

- Compared in two RCTs
- Similar results in pain relief at 1-2 years
- Improved pain relief in surgery (80%) vs. endoscopy (35%) at 5 years
  - 50% of subjects randomized to endoscopy ultimately underwent surgery

Cahen. Gastroenterology 2011;141:1690.
Dite. Endoscopy 2003;35:553.

Endocrine insufficiency

- Diabetes secondary to diseases of the exocrine pancreas (e.g., CP, pancreatic cancer, etc.) is classified as type 3c DM
- DM develops in >80% of CP at 25 years of follow-up
- Glycemic control is more "brittle" in type 3c DM due to decreases in counter-regulatory hormones
  - Glucagon and pancreatic polypeptide
- It's uncertain whether or not patients with type 3c DM benefit from a tailored anti-diabetic regimen

Rickels. Pancreatology 2013;13:336.
Malka. Gastroenterology 2000;119:1324.

Exocrine insufficiency

- Develops decades after onset of CP
- Fat maldigestion is most problematic due to the lack of significant redundancy in lipase
- Symptoms:
  - Severe – greasy, oily stools
  - Mild – bloating, flatulence
- Diagnosis is challenging due to the lack of a convenient and accurate test

Hart. Diagnosis of exocrine pancreatic insufficiency. Curr Treat Options Gastroenterol 2015 (epub).

Exocrine insufficiency - treatment

- Enzyme replacement is recommended in the presence of steatorrhea (>15g fat/24 hr)
- 90,000 USP units of lipase are necessary for normal fat digestion (10% of normal output)
- Recommended starting dose is 24-50,000 USP units of lipase/meal
- Lack of response: medication non-compliance, inadequate enzyme dosing, bacterial overgrowth, lactose intolerance, etc.

Forsmark. Gastroenterology 2013;144:1282.

Metabolic bone disease in CP

- High prevalence of metabolic bone disease in CP:
  - Osteopenia – 40%
  - Osteoporosis – 25%
- Increased risk of low-trauma fractures
- Traditional risk factors: smoking, alcohol, vitamin D deficiency
- Additional risk factor: CP induces an inflammatory state, which contributes to bone loss
- Screening should be considered for all CP patients

Duggan. Clin Gastroenterol Hepatol 2014;12:219.
Tignor…Conwell. Am J Gastroenterol 2010;105:2680.

Pancreatic cancer

- Cumulative lifetime incidence is up to 5%

Raimondi. Best Pract Res Clin Gastroenterol 2010;24:349.
Lowenfels. N Engl J Med 1993;328:1433.

Pancreatic cancer

- Cumulative lifetime incidence is up to 5%
- Increased risk of pancreatic cancer in CP compared to general population (pooled RR 13.3)
- There is a markedly increased risk in hereditary and tropical pancreatitis
- No current screening recommendations

Raimondi. Best Pract Res Clin Gastroenterol 2010;24:349.
Lowenfels. N Engl J Med 1993;328:1433.

Summary

- The diagnosis of chronic pancreatitis involves considering a patient's clinical history and pancreatic morphology and function
- Management of chronic pancreatitis is focused on screening and treating complications, including pain, diabetes, and fat maldigestion
- Metabolic bone disease is highly prevalent in chronic pancreatitis, and screening should be considered

Recommended reading

- Conwell DL. Chronic pancreatitis: making the diagnosis. Clin Gastroenterol Hepatol 2012;10:1088.
- Forsmark CE. Management of chronic pancreatitis. Gastroenterology 2013;144:1282.
- OSU patient-oriented symposium on CP: http://internalmedicine.osu.edu/digestivediseases/about-the-division/pancdisease/pancsymposium/index.cfm