

## **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.

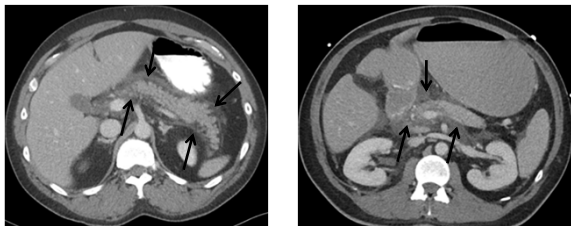
## Diagnosis of acute pancreatitis

## Diagnosis

- Two of the following are required:
  1. Typical upper abdominal pain
  2. Elevated lipase or amylase ( $>3\times$  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

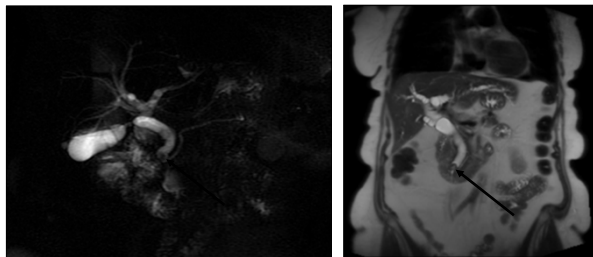
- Ampullary obstruction – gallstones, sludge, cancer, ampullary stenosis, parasites, (SOD)
- Toxins – EtOH
- Idiopathic
- Metabolic – hypertriglyceridemia, ↑ calcium
- Traumatic – post-ERCP, blunt trauma
- Congenital – choledochocoele, annular pancreas, (pancreas divisum)
- Genetic – PRSS1, (CFTR)
- 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	Class Ib	Class II	Class III
α-methylidopa	All-trans-retinoic acid	Acetaminophen	Aledronate
Azodisalicylate	Amiodarone	Chlorthalidone	Atorvastatin
Bezafibrate	Azathioprine	Clozapine	Carbamazepine
Cannabis	Clomiphene	DDI	Captopril
Carbamazole	Dexamethasone	Erythromycin	Ceftriaxone
Codeine	Ifosfamide	Estrogen	Chlorothalidone
Cytosine	Lamivudine	L-asparaginase	Cimetidine
Arabinoside	Losartan	Pegaspargase	Clarithromycin
Dapsone	Lynesterol/methoxyethinylestradiol	Propofol	Cyclosporin
Enalapril	6- MP	Tamoxifen	Gold
Furosemide	Meglumine		Hydrochlorothiazide
Isoniazid	Methimazole		Indomethacin
Mesalamine	Nelfinavir		Interferon/ribavirin
Metronidazole	Norethindronate/mestranol		Irbesartan
Pentamidine	Omeprazole		Isotretinoin
Pravastatin	Premarin		Ketorolac
Procainamide	Sulfamethazole		Lisinopril
Pyritinol	Trimethoprim-sulfamethazole		Metolozone
Simvastatin			Metformin
Stibogluconate			Minocycline
Sulfamethoxazole			Mirtazapine
Sulindac			Naproxen
Tetracycline			Paclitaxel
Valproic acid			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	Class V
Adrenocorticotrophic hormone	Octreotide
Ampicillin	Oxyphenbutazone
Bendroflumethiazide	Penicillin
Benzapril	Phenophthalein
Betamethazone	Propoxyphene
Capecytabine	Ramipril
Cisplatin	Ranitidine
Colchicine	Rifampin
Cyclophosphamide	Risperidone
Cyproheptidine	Ritonovir
Danazol	Roxithromycin
Diazoxide	Rosuvastatin
Diclofenac	Sertaline
Difenoxylate	Strychnine
Doxorubicin	Tacrolimus
Ethacrinic acid	Vigabatrin/lamotrigine
Famciclovir	Vincristine
Finasteride	
5-fluorouracil	
Fluvastatin	
Gemfibrozil	
Interleukin-2	
Ketoprofen	
Lovastatin	
Mefenamic acid	
Nitrofurantoin	

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
- Predictors of severity:**
- Advanced age
  - Obesity
  - SIRS
  - Organ failure
- Favorable prognosis:**
- 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
- Reasons to consider transfer to a high-volume center:
  - 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

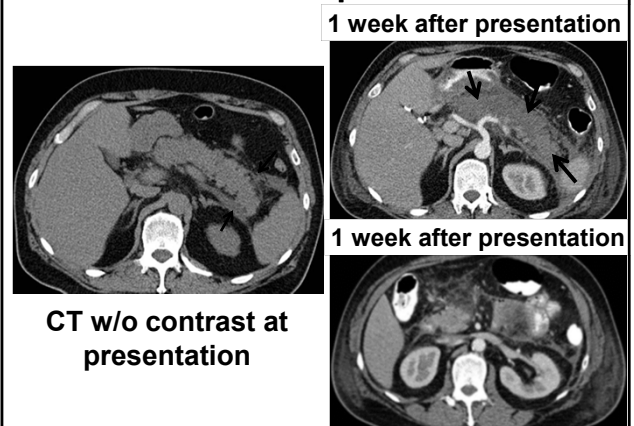
- Useful for management of gallstone pancreatitis:
  1. With cholangitis (emergent)
  2. Retained CBD stone, pre/post-cholecystectomy (urgent)
  3. Non-surgical candidate for cholecystectomy (non-urgent)

## Local complications (necrotizing pancreatitis)

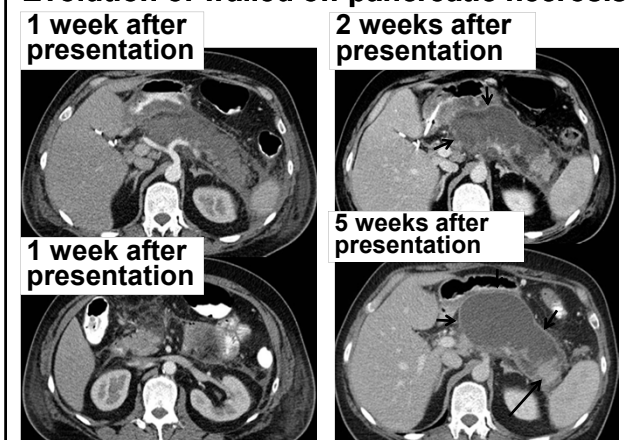
- **ACG:** Prophylactic antibiotics are NOT recommended for patients with sterile necrosis
- Not all patients with walled off pancreatic necrosis (WOPN) require intervention
- Approach to symptomatic (or infected) WOPN:
  - Delay (>4 weeks)
  - Drain
  - Debridement

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.

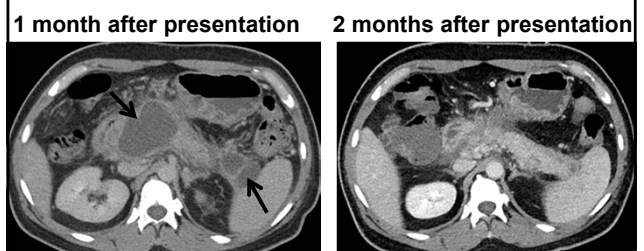
## Evolution of walled off pancreatic necrosis



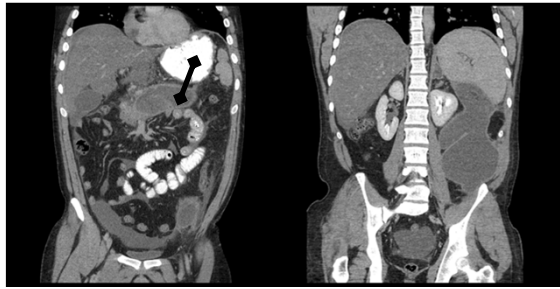
## Evolution of walled off pancreatic necrosis



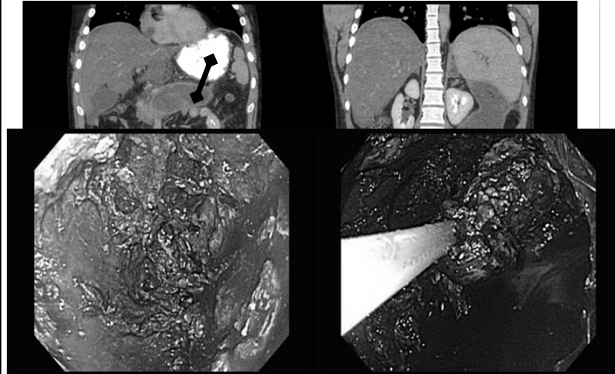
## Delay interventions, if clinically possible



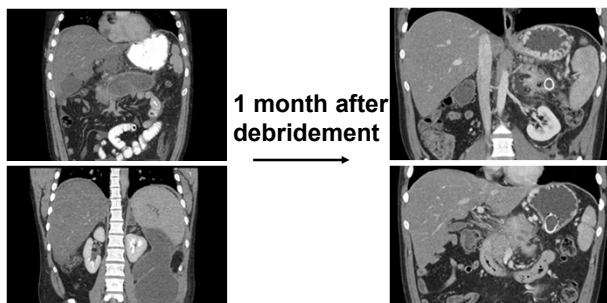
## Debridement (endoscopic)



## Debridement (endoscopic)



## Debridement (endoscopic)



## 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/acute pancreatitis/index.cfm>

## Chronic Pancreatitis

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## 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%

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- 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)

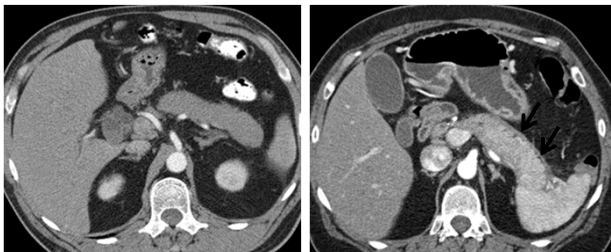
## Hereditary pancreatitis

- 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.

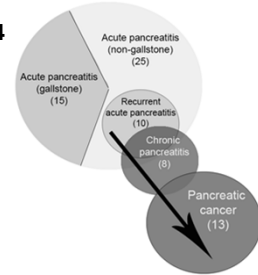
## Autoimmune pancreatitis (type 1 AIP)

- ~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

- $\geq 2$  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.

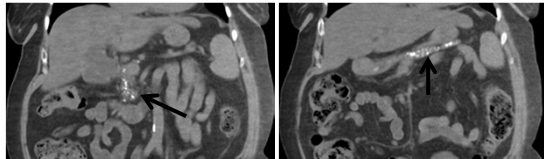
## Diagnostic modalities

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

Conwell DL. Pancreas 2014;43:1143.

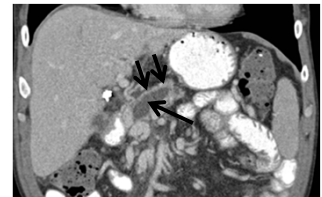
## CT for diagnosis of CP

- Helpful for identification of advanced CP



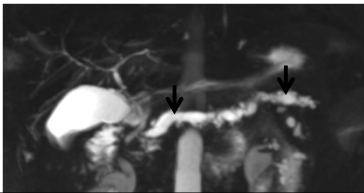
## CT for diagnosis of CP

- 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

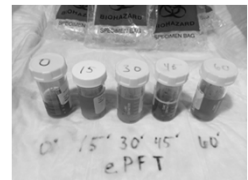
## EUS for diagnosis of CP

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

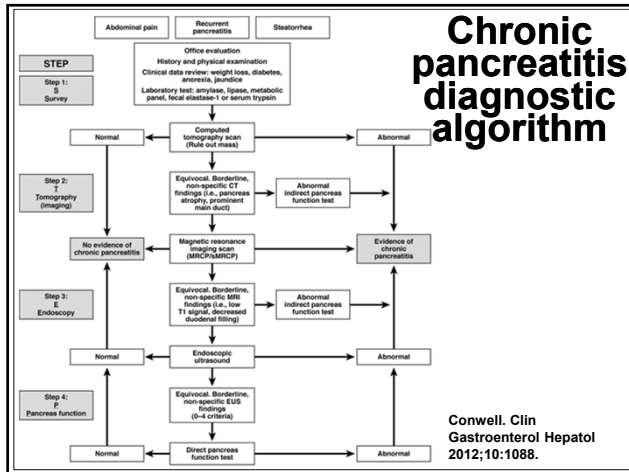
Stevens. Gastrointest Endosc Clin N Am 2013;23:735.

## 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.



## 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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## 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

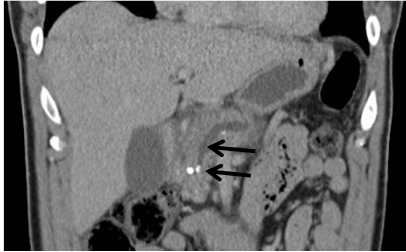
## Pain management: medical

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

Cohen. 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>