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

Diagnosis of acute pancreatitis

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

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

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

### Summary of Drug-Induced Acute Pancreatitis Based on Drug Class

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

#### Class Ib
- All-trans-retinoic acid
- Amiodarone
- Azathioprine
- Clomiphene
- Ifofamidone
- Lamivudine
- Losartan
- Methimazole
- Nelfinavir
- Norethindone/mestranol
- Premarin
- Sulfamethazole
- Sulfamethoxazole
- Trimethoprim/sulfamethazole

#### Class II
- Acetaminophen
- Chlorthiazide
- Clozapine
- DDI
- Erythromycin
- Estrogen
- L-asparaginase
- Pegaspargase
- Protopofol
- Tamoxifen
- Hydrochlorothiazide
- Indomethacin
- Interferon/ribavirin
- Ibesartan
- Isotretinoin
- Ketorolac
- Lisinopril
- Metolazone
- Metformin
- Minocycline
- Mirtazapine
- Naproxen
- Paclitaxel
- Prednisone
- Prednisolone

#### Class III
- Adrenocorticotropic hormone
- Ampicillin
- Bendroflumethiazide
- Benzapril
- Betamethasone
- Capecitabine
- Cisplatin
- Colchicine
- Cyclophosphamide
- Cyproheptidine
- Danazol
- Diazoxide
- Diclofenac
- Difenoxylate
- Doxorubicin
- Ethacrinic acid
- Famciclovir
- Finasteride
- 5-fluorouracil
- Fluvastatin
- Gemfibrozil
- Interleukin-2
- Ketoprofen
- Lovastatin
- Mefanamic acid
- Nitrofurantoin

#### Class IV
- Octreotide
- Oxyphenbutazone
- Penicillin
- Phenophthalein
- Prooxyphene
- Ramipril
- Ranitidine
- Rifampin
- Risperidone
- Ritonovir
- Roxithromycin
- Rosuvastatin
- Sertaline
- Strychnine
- Tacrolimus
- Vigabatin/lamotrigine
- Vincristine

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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)


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

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**BISAP, bedside index of severity in acute pancreatitis**

**HAPS, harmless acute pancreatitis score**

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### Revised Atlanta Criteria

<table>
<thead>
<tr>
<th></th>
<th>Organ failure</th>
<th>Local complications*</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild AP</td>
<td>No</td>
<td>No</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Moderately-severe AP</td>
<td>No or transient (&lt;48h)</td>
<td>Yes</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Severe AP</td>
<td>Persistent</td>
<td>Yes</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

*Local complication - pancreatic/extra-pancreatic necrosis

**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


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**Clinical management of AP**

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

**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


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**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.
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

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


Evolution of walled off pancreatic necrosis

CT w/o contrast at presentation

1 week after presentation

1 week after presentation
Evolution of walled off pancreatic necrosis

1 week after presentation

2 weeks after presentation

1 week after presentation

5 weeks after presentation

Delay interventions, if clinically possible

1 month after presentation

2 months after presentation
Debridement (endoscopic)

1 month after debridement

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

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

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 multidisciplinary approach
Recommended reading

- OSU patient-oriented symposium on AP: http://internalmedicine.osu.edu/digestivediseases/about-the-division/pancdisease/acutepancreatitis/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


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%
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- 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.)

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

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

Presentation One month after steroids

**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


**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

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


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

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

![MRI/MRCP Image](image)

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**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


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

Chronic pancreatitis diagnostic algorithm

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
Pain management in CP

• Pain accounts for significant medical costs and poor social function and QOL
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• Mechanisms for pain:
  • ductal obstruction
  • neural remodeling
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

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

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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


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

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.


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

Pancreatic cancer

• Cumulative lifetime incidence is up to 5%


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

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

• OSU patient-oriented symposium on CP: http://internalmedicine.osu.edu/digestivediseases/about-the-division/pancdisease/pancsymposium/index.cfm