Acute and Chronic Pancreatitis

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No Disclosures

Diagnosis of Acute Pancreatitis

Two of the following three features:

- Characteristic abdominal pain
- Amylase and/or lipase > 3 times upper limit of normal
- CT scan showing characteristic findings of AP

Acute Pancreatitis: Pathophysiology

- Clinical Presentation
  - Epigastric pain, nausea, vomiting
- Diagnosis
  - Clinical evaluation
  - Serology (amylase, lipase, LFTs)
  - Imaging – ULTRASOUND (early), CT (later)
- Prognosis
  - Ranson criteria < 48 h
  - APACHE II > 48 h
  - BISAP Score
  - BUN Trajectory

Acute Pancreatitis: Differential Diagnosis

- Mesenteric ischemia
- Perforated gastric or duodenal ulcer
- Biliary colic
- Dissecting aortic aneurysm
- Intestinal obstruction
- Inferior wall myocardial infarction

Acute Pancreatitis: Red Flags

- Tachycardia, hypotension
- Tachypnea, hypoxemia
- Hemocoagulation
- Oliguria
- Encephalopathy
Acute Pancreatitis: Ranson Criteria

<table>
<thead>
<tr>
<th>Admission</th>
<th>After 48 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Age &gt; 55 years</td>
<td>- Hct decrease &gt; 10%</td>
</tr>
<tr>
<td>- WBC &gt; 18,000 mm³</td>
<td>- Bilirubin increase &gt; 8 mg/dl</td>
</tr>
<tr>
<td>- Glucose &gt; 200 mg/dl</td>
<td>- Ca²⁺ &lt; 8 mg/dl</td>
</tr>
<tr>
<td>- LDH &gt; 550 IU/L</td>
<td>- Po₂ &lt; 60 mm Hg</td>
</tr>
<tr>
<td>- AST &gt; 120 IU/L</td>
<td>- Base deficit &gt; 4 mEq/L</td>
</tr>
<tr>
<td>- Negative fluid balance &gt; 5L</td>
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</tbody>
</table>

Acute Pancreatitis: Etiology

- Alcohol 35%
- Gastroenteritis 40%
- Idiopathic 10%
- Drugs
  - Azathioprine
  - Thiazides
  - DDIs
  - Bactrim
  - Pentamidine
  - Sulfamethoxazole
  - Valproic Acid
- Trauma
- Postoperative
- Hyperglycemia
- Hypocalcemia
- Infecious Agents
  - Mumps, Coxsackie
  - CMV, HIV, Latakisona, etc.
- Miscellaneous
  - Ductal Obstruction

Acute Pancreatitis: Mortality

![Mortality Graph](image)

The majority of patients with severe disease have from 3 to 5 criteria.

Acute Pancreatitis: CT Scan Definitions

- Interstitial Pancreatitis
  - Focal or diffuse enlargement of the pancreas with enhancement of the parenchyma in response to IV contrast
  - Blood supply maintained

- Necrotizing Pancreatitis
  - Diffuse or focal areas of nonviable pancreatic parenchyma
  - Blood supply lost

Acute Pancreatitis: CT Scan

![CT Scan Progression](image)

Day 1

Day 3
Acute Pancreatitis

- **Treatment**
  - Mild: Supportive care, IVFs, analgesics
  - Severe: CT Scan, Necrosis vs. Interstitial
    - Aggressive hydration, pain management
    - Percutaneous aspiration / gram stain
    - Surgical debridement
    - Antibiotics
    - Nutrition support
    - Gallstones – Emergent ERCP

- **Complications**
  - ARDS, ARF, SIRS
  - Pseudocyst (symptomatic), abscess (E coli)

Case 1: Acute Pancreatitis

On Hospital Day 3:

- 65 year old with persistent abd pain, fever, nausea, vomiting
- Exam: febrile 101.5, stable vital signs, tenderness, flank ecchymosis, rebound and absent bowel sounds
- Labs:
  - Serology amylase lipase >2,000
  - Liver chemistries normal
- Imaging:
  - Ultrasound: Normal gallbladder, bile ducts and pancreas head
  - CT scan: edematous pancreas with 30% non-enhanced area

Should we start prophylactic antibiotics?

Acute Pancreatitis: Pharmacologic Issues

- **Antimicrobial Use**

- **Feeding**
  - Enteral versus parenteral nutrition

Prophylactic Antibiotics: Meta-analysis

- No reduction in infected necrosis
- No reduction in mortality
- No reduction in non-pancreatic infections
- No reduction in surgical intervention
- No reduction in hospital stay

- 329 patients
- 6 RCTs

Case 1: Acute Pancreatitis

On Hospital Day 3:

- 65 year old with persistent abd pain, fever, nausea, vomiting
- Exam: febrile 101.5, stable vital signs, tenderness, flank ecchymosis, rebound and absent bowel sounds
- Labs:
  - Serology amylase lipase >2,000
  - Liver chemistries normal
- Imaging:
  - Ultrasound: Normal gallbladder, bile ducts and pancreas head
  - CT scan: edematous pancreas with 30% non-enhanced area

Should we start prophylactic antibiotics? NO
Case 1: Acute Pancreatitis

On Hospital Day 5:
- 65 year old with persistent abd pain, fever, nausea, vomiting
- Exam: febrile 101.5, stable vital signs, tenderness, flank echymosis, rebound and absent bowel sounds
- Labs:
  - Serology amylase lipase >2,000
  - Liver chemistries normal
- Imaging:
  - Ultrasound: Normal gallbladder, bile ducts and pancreas head
  - CT scan: edematous pancreas with 30% non-enhanced area

Should we feed patient? If so, what route delivery?

Acute Pancreatitis: Nutrition

- Activation of intracellular proteolytic enzymes
- Food further stimulates production of trypsin
- Cornerstone of AP mgmt: pancreatic rest
- Long-term resting ‘fasting’ the pancreas led to:
  - High rates of body nitrogen and protein loss
  - Increased mortality


Meta-analysis: Nutritional Support and Infection

1) Tissue repair and recovery
   - Hypermetabolic and catabolic disease state
   - Necrotizing disease: accelerated amino acid losses
2) Modulates inflammatory response
   - Partially generated within the gut lumen and mucosa
   - Prevention of intestinal ischemia
   - Prevention of luminal stasis and bacterial overgrowth


Meta-analysis: Endpoints

- Reduced hospital stay in enteral feeding groups (mean reduction 2.9days, p<0.001)

Should we feed patient? YES
If so, what route delivery? ENTERAL, jejunal preferred
Drug-Induced Pancreatitis


Obtain CT-guided FNA + Gram Stain (usually after 7-10 days)

May repeat FNA q5-7 days if clinically indicated

Targeted antimicrobial therapy

High suspicion of infected necrosis

Clinically stable

Clinically unstable

Prompt surgical debridement vs. delayed surgical or endoscopic debridement vs. no debridement

Pancreatic Necrosis (confirmed by CT scan)


Medical History 1700's

1788 Cawley reported a “free living young man” who died of emaciation and diabetes and whose postmortem examination revealed multiple pancreatic calculi

Marks IN, Bank S. Bockus Gastroenterology. 4th ed. 1985

Chronic Pancreatitis: Overview

• Progressive, irreversible damage
• Exocrine and endocrine cells
• Exocrine insufficiency – steatorrhea
• Endocrine insufficiency – diabetes
• Incidence 3.5 to 10 per 100,000 population

Pancreatic Steatorrhea

Mechanisms

- Decreased concentration of lipase and collagen
- Duodenal pH
- Inactivation of pancreatic lipase (pH 4.5)
- Production of bile salts

Stool with excessive fat

Subar stain

Pancreatic Steatorrhea

AGA, Gastroenterology Teaching Project 2006.

Chronic Pancreatitis

A. Computed tomography
B. Endoscopic retrograde pancreatography
C. Endoscopic ultrasound
D. Histology
### TIGAR-O

- **Toxic-metabolic**
  - Alcohol
  - Tobacco
  - Hypercalcemia
  - Chronic renal failure
  - Toxins
- **Idiopathic**
  - Early onset
  - Late onset
  - Tropical
- **Genetic**
  - Hereditary pancreatitis (cystic fibrosis transmembrane conductance regulator (CFTR) mutations)
  - SPINK 1 mutations
  - Alpha-1 antitrypsin deficiency
  - Autoimmune
  - Isolated autoimmune CP
  - Syndromic autoimmune CP (PSC, Sjögren's-associated, etc.)
- **Recurrent and severe AP**
  - Postnecrotic
  - Recurrent acute pancreatitis
  - Ischemic/vascular
- **Obstructive**
  - Pancreas divisum
  - Intrapapillary mucinous tumor
  - Ductal adenocarcinoma

### SAPE Hypothesis (Sentinel AP Event)

1. **Step A**: Acinar cell stimulation
   - Alcohol, gallstone, TG, oxidative stress
2. **Step B**: Sentinel Event
   - Early: pro-inflammatory response
   - Late: Stellate cells, pro-fibrotic response
3. **Step C**: Removal of stimulus
   - Abstinence
   - Cholecystectomy
   - Lipid lowering agents
4. **Step D**: Recurrent stimulation
   - Stellate cell mediated periacinar fibrosis

### CP Pain Neurobiology

- CP pain leads to changes in cortical projections of the nociceptive system
  - Gastroenterology 2007;132:1546-1556
- Probably the most important article in years on chronic pancreatic pain neurobiology. This publication has opened the door for further investigations in CP pain management
- CP pain includes activation and modulation of visceral afferents, descending pain pathways and central neuroplasticity. The degree of central sensitization was 17% in controls and 36% in CP patients.
  - Pancreas 2007; 35(1) 22-9
- Further evidence supporting neurobiology & central processing in CP pain
- Thorascopic splanchnicectomy reduces nociceptive visceral input as evidenced by a decreased narcotic requirement but appears to have no affect on central sensitization in CP patients by quantitative sensory testing.

### Chronic Pancreatitis

- **Pain Management**
- **Malabsorption**: exocrine dysfunction
- **Pancreatic Diabetes**: endocrine dysfunction

### Case 2: Chronic Pancreatitis

CE is a 58YOM presenting for evaluation of 1-yr hx of epigastric pain radiating to the back and 10lb wt loss. He describes the pain as constant, present on most days, often debilitating (10/10 pain scale), and oily bowel movements

- SH: alcohol consumption 5-6 beers/day for 25 years but reduced since onset pain
- Normal CBC, electrolytes, liver chemistries, amylase, and lipase
- Upper GI endoscopy: no signs PUD
- CT abdomen: scattered parenchymal calcifications, dilation of main pancreatic duct to 5 mm max diameter, no mass

1. What are the pharmacologic options for pain management?
Pain Management:
Step-wise Management

- Low-fat diet, non-narcotic analgesics, no alcohol
- Therapeutic trial of enzyme
  - 1-2 months, reassess pain
  - Dose: 16,000-64,000 units lipase qAC
- Narcotic analgesia
- Endoscopic, surgical management


Case 2: Chronic Pancreatitis

1. What are the pharmacologic options for pain management?

Reasonable to:
- Initiate a trial of pancreatic enzymes
- If failed response:
  - Analgesics +/- pain modifying agents
  - Endoscopic therapy
  - Surgery


Chronic Pancreatitis

- Pain Management

- Malabsorption: exocrine dysfunction

- Pancreatic Diabetes: endocrine dysfunction


Pancreatic Enzyme Replacement Therapy

- Mechanism for steatorrhea:
  - ↓ Lipase synthesis
  - Lipase denaturation

- Fat digestion by lipase:
  - Healthy subjects:
    - Gastric lipase activity
    - Lipase activity ≈10% total lipase activity
  - CP:
    - Gastric lipase activity
    - 90% of all lipase activity
    - Unable to compensate for all lipid digestion required


Pancreatic Enzyme Pharmacotherapy

Commercially available pancreatic enzyme preparations:
- Creon
- Zenprep

Pancreatic Enzyme Pharmacotherapy

1. Conventional, uncoated:
   - Susceptible to inactivation by acidity of stomach
     - Increase dose
     - Acid suppressive therapy

2. Enteric-coated microencapsulated:
   - pH-sensitive coating
   - Microspheres, minimicrospheres, microtablets
   - Distribution in chyme throughout gastric emptying

3. Enteric-coated, high buffered
   - Contain bicarbonate

Treatment Regimens: Malabsorption

- Dose approximated by lipase content
  - Mean duodenal lipase activity: 40-60 units/mL
    - Adults: ~25,000-40,000 units lipase/meal
    - Children, adolescents: ~500-2000 units lipase/kg/meal (or 500-4000 units lipase/g fat)

- Goal:
  - Reduce steatorrhea to <15g/day of fat
  - Titrate dose based to effect

- Considerations if treatment failure:
  - Check compliance
  - Product integrity
  - Acid suppression

Chronic Pancreatitis

- Pain Management

- Malabsorption: exocrine dysfunction

- Pancreatic Diabetes: endocrine dysfunction

Pancreatic Diabetes

- Glucose intolerance
  - Overt diabetes: late in the course of disease

- Pancreatic diabetes:
  - Typically insulin-requiring
  - Different from type 1 diabetes
    - Pancreatic alpha cells also affected
    - May lead to increased risk hypoglycemia

Treatment Options for CP

- “Good”
  - Anatomy based
  - Macroscopic

- “Better”
  - Physiology based
  - Microscopic

- “Best”
  - Pathogenesis based
  - Molecular

Pathogenesis Based Therapy: “Best”

- Pancreatic stellate cells
  - Activation

- Molecular mediators
  - TGF-β, PDGF
  - Pro-inflammatory cytokines
    - IL-1, IL-6, TNF-alpha

- Molecular pathways
  - MAPK, PI3K

- Novel molecular targets

- Potential therapeutic agents
Question 1
• Enteric coated enzymes are preferable over uncoated enzymes in the management of steatorrhea?
  • A. True
  • B. False

Answer A: True
– Protection of lipase from low pH in stomach

Question 2
• Which of the following diagnostic tests has the highest accuracy at detecting early/mild chronic pancreatitis?
  • A. ERCP
  • B. MRCP
  • C. Pancreas function test
  • D. EUS

Answer: C, Pancreas Function Test

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sxs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abd Pain</td>
<td>(10y)</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steatorrhea (20y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>(30y)</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>(55y)</td>
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<table>
<thead>
<tr>
<th>Function</th>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERCP</td>
<td>Normal</td>
<td>Minimal</td>
</tr>
<tr>
<td>MRCP</td>
<td>Normal</td>
<td>T1 signal</td>
</tr>
<tr>
<td>EUS</td>
<td>0-2</td>
<td>3-4</td>
</tr>
</tbody>
</table>

Question 3
• Which of the following is not part of the Ranson Criteria for assessment of Acute Pancreatitis Severity?
  • WBC
  • Gender
  • Age
  • Glucose
  • LDH

Answer C: Gender

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<th>Admission</th>
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<tr>
<td>Age &gt; 60 y</td>
<td>+10 dec. -10%</td>
</tr>
<tr>
<td>WBC &gt; 15,000/mL</td>
<td>+5</td>
</tr>
<tr>
<td>BUN &gt; 16 mg/dL</td>
<td>+5</td>
</tr>
<tr>
<td>GFR &lt; 60 mg/dL</td>
<td>+5</td>
</tr>
<tr>
<td>PaO2 &lt; 60 mmHg</td>
<td>+5</td>
</tr>
<tr>
<td>Base diff &gt; 6 mmHg</td>
<td>+5</td>
</tr>
<tr>
<td>Negative fluid balance &gt; 10 L</td>
<td>+5</td>
</tr>
</tbody>
</table>
# Pancreatitis Resources

- **Harrisons and Cecil’s Textbooks of Medicine**
- **Practice Guidelines for Acute Pancreatitis:**
  - American College of Gastroenterology
  - American Gastroenterological Association
    - Practice guidelines for acute pancreatitis, pain management in chronic pancreatitis
- **Gastroenterology Clinics of North America:**