Chronic Pancreatitis

Dhiraj Yadav, MD MPH
Associate Professor
Division of Gastroenterology & Hepatology
University of Pittsburgh Medical Center

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Acute Pancreatitis

• Acute Inflammatory condition
• Duration: days to weeks
• Recovery in most patients
• Clinical Presentation
  – Sudden onset of upper abdominal pain
  – Elevation of serum pancreatic enzymes to ≥3 times the upper limit of normal
  – Imaging evidence
Acute Pancreatitis - Etiology

• **Gallstones**

• **Alcohol**
  • Idiopathic  *(CFTR mutations in some)*
  • Hypertriglyceridemia
  • Medications
  • Post-ERCP
  • Hereditary pancreatitis
  • Hypercalcemia
  • PD obstruction
  • Other rare causes
Normal Pancreas

Interstitial AP

Necrotizing AP
Chronic Pancreatitis

- Chronic inflammatory condition
- Usually irreversible damage of the pancreas
- Clinical Presentation
  - **Acute Pancreatitis**
  - **Pain**
    - Exocrine insufficiency (Steatorrhea – Fatty stools)
    - Endocrine insufficiency (Diabetes)
  - Complications
    - Pseudocysts
    - Biliary obstruction
    - Gastric outlet obstruction
    - Pancreatic ascites
    - Uncommon complications
Diagnosing Chronic Pancreatitis
### Disease burden

**Approximate US Estimates**

- **Acute Pancreatitis**
  - Episodes: 275,000
  - Incident cases: 150,000

- **Chronic Pancreatitis (based on definition)**
  - Incident cases: 20,000-30,000
  - Prevalent cases:
    - 175,000-250,000

- **Pancreatic cancer (2013)**
  - Incident cases: 45,220
  - Deaths: 38,460

Gastroenterology 2013;144:1252-61
## Current Etiology of Chronic Pancreatitis

<table>
<thead>
<tr>
<th>Etiology (%)</th>
<th>All (n=539)</th>
<th>Female (n=256)</th>
<th>Male (n=283)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NAPS2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>44.5</td>
<td>28.1</td>
<td>59.4</td>
</tr>
<tr>
<td>Genetic</td>
<td>8.7</td>
<td>12.5</td>
<td>5.3</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>2.2</td>
<td>2.3</td>
<td>2.1</td>
</tr>
<tr>
<td>Obstructive</td>
<td>8.7</td>
<td>12.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Other</td>
<td>7.2</td>
<td>9.0</td>
<td>5.7</td>
</tr>
<tr>
<td><strong>Idiopathic</strong></td>
<td>28.6</td>
<td>35.2</td>
<td>22.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Etiology (%)</th>
<th>All (n=893)</th>
<th>Female (n=233)</th>
<th>Male (n=660)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PanCroInAISP (Italian Survey)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>34</td>
<td>10</td>
<td>42</td>
</tr>
<tr>
<td>Obstruction</td>
<td>27</td>
<td>46</td>
<td>20</td>
</tr>
<tr>
<td>Alcohol + Obstruction</td>
<td>9</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>4</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Dystrophy</td>
<td>6</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Hereditary/Genetic</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td><strong>Idiopathic</strong></td>
<td>17</td>
<td>25</td>
<td>14</td>
</tr>
</tbody>
</table>

# Genetics and Chronic Pancreatitis

<table>
<thead>
<tr>
<th>Gene Name</th>
<th>Consequence</th>
<th>Prevalence (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cationic Trypsinogen (PRSS1)</td>
<td>↑Trypsinogen activation, ↓Trypsin degradation</td>
<td>&lt;0.01</td>
<td>Penetrance - AP 80%, CP 40%</td>
</tr>
</tbody>
</table>
| Pancreatic Secretory Trypsin Inhibitor (SPINK1)   | Failure of Trypsin degradation                                               | 2-3            | • Acute phase protein  
• Risk related to one/two mutations, another risk factor  
• Risk higher in non-alcoholic CP |
| Chymotrypsin C (CRTC)                             | Failure of Trypsin degradation                                               | ≤1             | - Risk higher in Tropical/Idiopathic CP                                                           |
| Calcium Sensing Receptor (CASR)                   | ↑Extracellular ionized calcium; other ?                                      | 10             | Role in alcohol-related pancreatitis                                                               |
| Cystic Fibrosis Transmembrane Conductance (CFTR)  | Impaired flushing of pancreatic ducts leads to Trypsin activation           | 2-3 (Δ508)      | • Risk in PS patients: ~25%  
• ICP: Compound heterozygotes  
• Role of “Atypical/Benign” mutations (e.g. R75Q, etc.) |
| Claudin-2                                         | ?                                                                           | 26             | • Present on X chromosome  
• Increases risk of progression from Acute to Chronic Pancreatitis                                 |
Diagnosing Chronic Pancreatitis: CT scan
Diagnosing Chronic Pancreatitis: MRI/MRCP
Diagnosing Chronic Pancreatitis: EUS
Diagnosing Chronic Pancreatitis: Pancreatic Function Testing

• Hormone stimulation test
  – Secretin
  – Cholecystokinin (CCK)

• Stool testing
  – Fecal Elastase
  – Fecal Chymotrypsin
QOL in Chronic Pancreatitis is similar or worse than many chronic diseases
Physical QOL is profoundly affected by CP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Category</th>
<th>Parameter Estimate</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>—</td>
<td>52.81</td>
<td>1.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CP</td>
<td>Control subjects</td>
<td>-12.02</td>
<td>0.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age 50 y*</td>
<td>—</td>
<td>-0.16</td>
<td>0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>Male</td>
<td>-1.60</td>
<td>0.67</td>
<td>0.01</td>
</tr>
<tr>
<td>White</td>
<td>Others</td>
<td>0.94</td>
<td>0.92</td>
<td>0.30</td>
</tr>
<tr>
<td>Current BMI 25 kg/m²†</td>
<td>—</td>
<td>-0.29</td>
<td>0.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drinking category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light-moderate</td>
<td>Abstainer</td>
<td>2.57</td>
<td>0.83</td>
<td>0.002</td>
</tr>
<tr>
<td>Heavy—very heavy</td>
<td></td>
<td>0.63</td>
<td>1.00</td>
<td>0.53</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>Never smoker</td>
<td>-0.51</td>
<td>0.84</td>
<td>0.55</td>
</tr>
<tr>
<td>Current</td>
<td></td>
<td>-3.03</td>
<td>0.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>No diabetes</td>
<td>-3.36</td>
<td>0.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart attack or stroke</td>
<td>—</td>
<td>-2.26</td>
<td>1.27</td>
<td>0.08</td>
</tr>
<tr>
<td>Gallstones or gallbladder removal</td>
<td>No gallstones or gallbladder removal</td>
<td>-2.71</td>
<td>0.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CP† age 50 y</td>
<td>—</td>
<td>0.18</td>
<td>0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CP‡ current BMI</td>
<td>—</td>
<td>0.39</td>
<td>0.12</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Final sample size: control subjects n = 570 (93%); CP n = 431 (97%). Adjusted $R^2 = 37.7\%$. For drinking category definitions, refer to Methods. PCS score for a 50-year-old male white control subject with a BMI of 25 kg/m² who is an abstainer, never smoker, and has no comorbidities will be 53.75. A CP patient with similar characteristics will have a PCS score of 41.73.

Pancreas 2013;42:293-300
Mental QOL is significantly lowered by CP

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</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td></td>
<td>52.39</td>
<td>1.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CP</td>
<td>Control subjects</td>
<td>-4.24</td>
<td>0.90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age 50 y*</td>
<td>—</td>
<td>0.09</td>
<td>0.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>Male</td>
<td>-1.53</td>
<td>0.67</td>
<td>0.02</td>
</tr>
<tr>
<td>White</td>
<td>Others</td>
<td>0.51</td>
<td>0.92</td>
<td>0.58</td>
</tr>
<tr>
<td>Current BMI 25 kg/m²†</td>
<td>—</td>
<td>-0.03</td>
<td>0.06</td>
<td>0.64</td>
</tr>
<tr>
<td>Drinking category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Abstainer</td>
<td>0.73</td>
<td>0.83</td>
<td>0.37</td>
</tr>
<tr>
<td>Heavy–very heavy</td>
<td></td>
<td>-1.09</td>
<td>1.01</td>
<td>0.28</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>Never smoker</td>
<td>-0.15</td>
<td>0.85</td>
<td>0.86</td>
</tr>
<tr>
<td>Current</td>
<td></td>
<td>-2.45</td>
<td>1.08</td>
<td>0.02</td>
</tr>
<tr>
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<td>No diabetes</td>
<td>-0.10</td>
<td>0.86</td>
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<td>-0.91</td>
<td>0.78</td>
<td>0.24</td>
</tr>
<tr>
<td>CP‡ current smoking</td>
<td>—</td>
<td>-3.85</td>
<td>1.43</td>
<td>0.007</td>
</tr>
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Final sample size: control subjects n = 570 (93%); CP n = 431 (97%). Adjusted $R^2 = 18.8\%$. For drinking category definitions, refer to Methods. MCS score for a 50-year-old male white control subject with a BMI of 25 kg/m², who is an abstainer, never smoker, and has no comorbidities will be 52.90. A CP patient with similar characteristics will have a PCS score of 48.66.
Pain Patterns in Chronic Pancreatitis

• Many Types
  – Temporal nature: constant/intermittent
  – Severity: mild-moderate/severe
Chronic Pancreatitis - What are we treating?

• Pain
  – Attacks of acute pancreatitis
  – Disease flares w/o acute pancreatitis
  – Chronic pain
  – Other reasons – Pseudocyst, biliary obstruction, etc.

• Exocrine and endocrine insufficiency

• Other complications
  – Gastric outlet obstruction
  – Pancreatic ascites
  – Uncommon complications
Pain in Chronic Pancreatitis: Evaluation

• Cross-sectional imaging (assess morphology/complications)
  – Contrast enhanced CT scan (pancreas protocol – if possible)
  – MRI/MRCP (with secretin – if possible)
  – Endoscopic ultrasound – depending on individual situation

• Think about and exclude non-pancreatic causes

• Understanding the natural history of pain (pattern, severity, temporal nature) is important in making all decisions

• Multidisciplinary approach is preferred

• Endoscopic therapy and surgery should be performed by individuals with specific interest and experience
Pain in Chronic Pancreatitis: Options

- General measures (ALL PATIENTS)
  - Behavior modification
  - Control of metabolic factors
- Analgesics – Stepwise approach
  - Nonnarcotics (e.g. NSAIDS)
  - Narcotic
    - Weaker, mixed agonist-antagonist or partial agonist (e.g. Tramadol)
    - Stronger narcotic (e.g. morphine, hydrocodone)
    - Neuromodulating agent (e.g. Pregabalin)
- Endoscopic therapy
- Surgery
- No proven benefit
  - Oral pancreatic enzyme supplementation
  - Antioxidants
  - Celiac plexus block
Progression of alcoholic AP to CP is NOT inevitable

Progression is influenced by continued alcohol consumption

<table>
<thead>
<tr>
<th>Alcohol consumption</th>
<th>Recurrent pancreatitis</th>
<th>Transition to CP</th>
<th>Complication with DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete cessation</td>
<td>19.8%</td>
<td>13.6%</td>
<td>14.1%</td>
</tr>
<tr>
<td>Decreased but occasional</td>
<td>18.9%</td>
<td>12.3%</td>
<td>14.2%</td>
</tr>
<tr>
<td>Decreased but daily</td>
<td>36.7%</td>
<td>23.3%</td>
<td>30.0%</td>
</tr>
<tr>
<td>Continue drinking as before</td>
<td>57.7%(^a)</td>
<td>40.9%(^a)</td>
<td>37.2%(^a)</td>
</tr>
</tbody>
</table>

\(^a\)Significant against upper 2 rows of data \(P < .05\).

Follow up information on alcohol consumption \(n=450\):
Complete cessation (39.3%); Decreased but occasional (23%)
Decreased but daily (6.7%); Continued drinking as before (30.4%)

Clin Gastroenterol Hepatol 2009;7:S15-7
Smoking and Chronic Pancreatitis

- Increases the risk of pancreatitis
- Associated with progression of pancreatitis
- Smoking cessation decreases the risk of progression

NAPS2 STUDY
Physicians under recognize smoking as a CP risk factor

Modified from Pancreatology 2010;10:713-19
Painless Chronic Pancreatitis

• Conservative management
• No need for endoscopic therapy or surgery, except:
  – Complications
  – Role in mild-moderate CP and minimal pain

• Morphological appearance of the pancreas does not correlate with subjective pain experience
Painless Chronic Pancreatitis

53 year M; Idiopathic chronic pancreatitis; smoker; exocrine insufficiency; borderline diabetes
Painless Chronic Pancreatitis

60 year F; diabetic x 15 years; Roux-en-Y gastric bypass 6 years ago; presents with mild constant pain and diarrhea not classical for steatorrhea
Pain in Chronic Pancreatitis: Medical Management

- No inflammatory mass
- No pancreatic ductal dilatation, stricture(s)
- No peripancreatic complications
- Refuses endoscopic therapy/surgery when indicated
Painful Chronic Pancreatitis

30 year M; CFTR mutations; RAP; pain; no exocrine/endocrine insufficiency
Painful Chronic Pancreatitis

26 year M; heavy alcohol use and smoking; multiple admissions for exacerbations and RAP; rapid progression to calcifications; recent diabetes; no clinical steatorrhea
71 year M; acute on chronic pancreatitis with significant peripancreatic necrosis
Acute on Chronic Pancreatitis

42 year F; alcoholic chronic pancreatitis with ongoing pain symptoms and frequent flares
Pain in Chronic Pancreatitis: Endoscopic Therapy (+/- ESWL)

- Pancreatic ductal dilatation and/or stricture(s)
- Symptomatic pseudocysts
- Biliary stricture (usually temporary)
56 year F; heavy alcohol use and smoking; has frequent flare ups and now constant pain

Painful Chronic Pancreatitis
62 year M; heavy alcohol use and smoking; presents with 2 recent exacerbations of AP
Painful Chronic Pancreatitis

52 year F; heavy alcohol use and smoking; RAP (6-7 admissions over 10 years); 2 admissions in the past year; asymptomatic between episodes
54 year M; heavy alcohol and smoking; hx RAP; escalating symptoms in the preceding few months
Painful Chronic Pancreatitis

40 year F; smoker; hx RAP; escalating symptoms over the past year
37 year M; alcoholic recurrent acute on chronic pancreatitis; disconnected duct due to central necrosis; frequent recurrences with persistent pseudocyst in head/neck area
Pain in Chronic Pancreatitis: Surgery

• Failed endoscopic therapy (usually)
  – Use as first line in –
    • Pancreatic ductal stones with heavy stone burden, especially in the body/tail region, usually with pancreatic ductal dilatation and stricture(s)

• Inflammatory mass (typically in pancreatic head)

• Biliary stricture

• Symptomatic pseudocysts (not amenable or after failed endoscopic therapy)
Chronic Pancreatitis: Surgery

- Resection
- Drainage
- Combination
Other options

Total Pancreatectomy with Islet AutoTransplantation (TPIAT)
Biliary stricture

33 year M; heavy alcohol use and smoking; hx RAP; presents with another flare and abnormal LFTs
Pseudoaneurysm
Exocrine and Endocrine Insufficiency

• Exocrine Insufficiency
  – Often undertreated
  – Timing with meals
  – Clinical history of steatorrhea seen in severe insufficiency
  – Fat soluble vitamin deficiencies

• Endocrine Insufficiency (Type 3c Diabetes)
  – Often needs Insulin treatment
Chronic Pancreatitis with Pain

Assess Morphology (CECT ± MRI/MRCP ± EUS)
Exclude other causes (EGD)

Pseudocyst >> ET/Surgery
CBD stricture >> ET/Surgery
PUD >> Medical Treatment
Pancreatic cancer >> Appropriate Rx

Trial of Conservative Treatment
Alcohol abstinence, smoking cessation
Analgesics – Pain clinic evaluation
Oral Pancreatic enzymes
Antioxidants

Morphology amenable to ET and/or Surgery

Yes
ET
Surgery

No
Continue conservative Rx
Celiac Plexus Block/other nerve ablation

ET is usually the first line except for *
ET is also used preoperatively as “Bridge to surgery” in specific situations
Options in *italics* have questionable/unclear benefit

After failed ET
Heavy stone burden*
Inflammatory mass*

Surgical Resection

Modified from Gastroenterology 1998,115:763-64
**Natural History of Chronic Pancreatitis**

- Pain relief
  - “Burn out” controversial
- Survival lower than general population
- Deaths mostly from non-pancreatic diseases
- Risk of cancer

Am J Gastroenterol 2012;106:2192-99
Autoimmune Pancreatitis

• **Clinical presentation mimics Pancreas cancer**
  • Less common
    • Pancreatitis, persistent pancreatic mass, scarred or shrunken pancreas, malabsorption
  • Elevation of serum IgG4 levels
  • Typical appearance on imaging tests and biopsy
  • Patients often have involvement of other organs
  • Two forms have been recognized - Type I and II
  • Excellent response to steroids

GCNA 2008;37:439-60; Pancreas 2012;41:835-9; Pancreas 2011;40:352-8
Autoimmune Pancreatitis
Autoimmune Pancreatitis
IgG4 related Disease
Take Home Points

• The spectrum of risk factors for CP have broadened
• Treatment of pain in CP needs a multidisciplinary approach
• Cross sectional imaging helps to assess pancreatic morphology and guides management
• An initial conservative approach is reasonable in all patients with painful CP
• When appropriate endoscopic therapy/surgery should be considered for pain relief
• TPIAT should be considered when appropriate/indicated
• Autoimmune Pancreatitis is a unique form of CP with excellent response to steroids