Pancreatitis

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Chronic pancreatitis

- Chronic pancreatitis (CP) is a progressive inflammatory disease of the pancreas, which leads to irreversible morphological changes (parenchymal atrophy & fibrosis) and impairment of exocrine and endocrine function
- Alcohol overconsumption is most frequent cause (70%)
- But 90% of alcoholics never get CP
- Genetic predisposition & environmental factors
- 25% of cases are idiopathic
- Several classification schemes have been proposed, each with different focus on clinical, imaging and morphological features
Classification of chronic pancreatitis

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Outcome</th>
<th>Morphology</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Alcohol abuse</td>
<td>Recovery</td>
<td>Small fat necrosis</td>
<td>Alcoholic mild acute pancreatitis</td>
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<td>Extensive fat, hemorrhagic necrosis</td>
<td>Alcoholic severe acute pancreatitis</td>
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<td>Recurrent pain</td>
<td>Alcoholic early stage chronic pancreatitis</td>
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<td>Functional insufficiency</td>
<td>Alcoholic advanced chronic pancreatitis</td>
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<td>Gallstone disease</td>
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<td>Diffuse peribiliary fibrosis, pseudocyst</td>
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<td>Scattered acinar necrosis</td>
<td>Infectious acute pancreatitis</td>
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<td>Distal peribiliary fibrosis, pseudocyst, calculi</td>
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<td></td>
<td>Without local and systemic complications</td>
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<td>Hereditary, familial</td>
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<td>Like alcoholic acute pancreatitis</td>
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<td>Peribiliary and peripancreatic fibrosis, duct dilatation</td>
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<td>Hereditary acute mild severe pancreatitis</td>
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<td></td>
<td>Hereditary chronic pancreatitis</td>
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<tr>
<td>Shock or drug misuse</td>
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<td>Like alcoholic acute pancreatitis</td>
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<td>Shock-toxic pancreatitis</td>
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<td>Hypergammaglobulinemia</td>
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<td>Like alcoholic acute pancreatitis</td>
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<td></td>
<td>Autoimmune pancreatitis</td>
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<td>Steatosis, common bile duct, stenosis of pancreatic duct</td>
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<tr>
<td>Hypercalcaemia</td>
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<td>Periductal lymphoplasmacytic infiltration, sclerosis</td>
<td>Metabolic pancreatitis</td>
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<td></td>
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<td>Stenosis of common bile duct, stenosis of pancreatic duct</td>
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<td>Infectious acute pancreatitis</td>
<td>Paradoxonal pancreatitis</td>
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<td>Recurrent pain of local complications</td>
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<td>Like alcoholic acute pancreatitis</td>
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<td></td>
<td>Infectious acute pancreatitis</td>
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</tbody>
</table>

*Because idiopathic pancreatitis is by definition not associated with a special etiology, it is not considered in this classification.*

Klöppel G. J Gastroenterol 2007; 42 (suppl 17): 55-57
Surgical resections for CP

- Performed for intractable pain in late-stage disease
- Specimens of ‘burnt-out’ chronic pancreatitis with scanty inflammatory cell infiltrate, almost completely absent pancreatic parenchyma, and marked fibrous tissue
- Extensive tissue sampling to exclude malignant transformation in CP
- Frey, Beger & Peustow procedures: aim to decompress the pancreatic duct system, which is thought to be a major cause of pain in CP


Frey procedure

- Core out 4-12g of diseased tissue from pancreatic head, leaving a ‘tissue crater’. Jejunal loop is anastomosed over the tissue crater and longitudinally opened pancreatic duct

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Beger procedure

- Most of head and part of body of pancreas are resected, leaving thin crescent of head and the intrapancreatic CBD in situ. Jejunal loop is anastomosed on the transection margins of the remnant head and body

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Puestow procedure

- Expose main pancreatic duct from neck to tail. Jejunal loop is anastomosed to anterior pancreatic surface to allow drainage of main and secondary pancreatic ducts over a length of 8-10cm

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Chronic pancreatitis

- Diffuse or localised
- Early stages, pancreas indurated and enlarged
- Later stages, rock hard and shrunken
- Duct dilatation/calculi
- Calcified deposits in pancreas or peripancreatic tissue, due to calcification in previous fat necrosis
- Pseudocysts

Chronic pancreatitis - microscopy

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Chronic pancreatitis - microscopy

Pseudocysts
- Collection of pancreatic juice secondary to duct rupture
- Occur in acute and chronic pancreatitis
- Thin walled in acute pancreatitis, thicker wall in chronic pancreatitis
- Unilocular, fluid-filled, no septations/mural nodules/excrences
- No epithelial lining
- Granulation tissue and (over time) fibrosis

Pseudocyst

Pancreatitis
- Autoimmune pancreatitis
- Groove pancreatitis/paraduodenal pancreatitis
- Hereditary chronic pancreatitis

Autoimmune pancreatitis (AIP)
- Concept of AIP introduced in 1995
- Sclerosing chronic pancreatitis or non-alcoholic duct destructive chronic pancreatitis
- Chronic fibroinflammatory disease
- Autoimmune pathogenesis, but cause unclear
- Responds to steroid therapy
  Shimosegawa et al. Pancreas 2011; 40: 352-8
- Spontaneous regression in 40% of AIP
- 10% of patients with chronic pancreatitis
  Chari et al. Pancreas 2010; 39: 540-54
  Shimosegawa et al. Pancreas 2011; 40: 352-8
  Zhang et al. Pancreas 2011; 40: 1172-9
  Deshpande et al. Mod Pathol 2012; 25: 1185-92

Autoimmune pancreatitis
- Clinically: abdominal pain (less severe than in other forms of CP), weight loss, obstructive jaundice
- PDAC is main clinical differential diagnosis
- Imaging: diffuse sausage-shaped enlargement with rim enhancement or focal lesion
- Heterogeneous disease with 2 subtypes: type 1 AIP (more common worldwide) and type 2 AIP, which have distinct clinical and histological features
### Autoimmune Pancreatitis

<table>
<thead>
<tr>
<th>Autoimmune Pancreatitis</th>
<th>Type 1 AIP</th>
<th>Type 2 AIP</th>
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<tbody>
<tr>
<td>Age of presentation</td>
<td>70 decades</td>
<td>40 decades</td>
</tr>
<tr>
<td>Gender distribution</td>
<td>predominantly male</td>
<td>equal</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>70%</td>
<td>50%</td>
</tr>
<tr>
<td>Infiltration</td>
<td>usually</td>
<td>usual</td>
</tr>
<tr>
<td>Acinar injury</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Imaging</td>
<td>50%</td>
<td>30%</td>
</tr>
<tr>
<td>Diffuse or segmental</td>
<td>usually</td>
<td>rare</td>
</tr>
<tr>
<td>Carcinomatosis</td>
<td>usually</td>
<td>rare</td>
</tr>
<tr>
<td>Extra-pancreatic organs</td>
<td>present</td>
<td>rare</td>
</tr>
<tr>
<td>Associated autoimmune</td>
<td>25%</td>
<td>up to 50%</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>common</td>
<td>rare</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>common</td>
<td>rare</td>
</tr>
</tbody>
</table>

Adapted from Raghuram & Chari. Curr Gastroenterol Rep 2012; 14: 95-105

### AIP - Macroscopy
- Diffusely enlarged pancreas
- Loss of normal lobulation
- May be only focal involvement – mass
- Narrowing of pancreatic duct
- Intrapancreatic CBD may also be narrowed
- Peripancreatic LNs may be enlarged

### AIP - Microscopy
- Periductal lymphoplasmacytic infiltrate (narrowed, star-shaped duct lumen)
- Inflammation of acinar parenchyma
- Patchy distribution of the inflammatory changes

### Autoimmune Pancreatitis

### Type 1 AIP - Microscopy
- Storiform fibrosis
- Fibro-inflammation extends into peripancreatic tissue
- Obliterative phlebitis, which probably starts as a perivenulitis
- Lymphoid aggregates
- IgG4 plasma cells
**Type 2 AIP - microscopy**
- Granulocytic epithelial lesion (GEL)  
  Köppel G. Mod Pathol 2007; 20: 6113-31
- Scantly or absent IgG4 plasma cells

**IgG4 immunostaining**
- Different threshold values ranging from >10 to >50 IgG4+ plasma cells/hpf have been proposed
- >10/hpf for biopsies, >50/hpf for resection specimens
- Distribution of IgG4+ plasma cells is patchy
- Count best performed in ‘hot spot’
- Average counted in three x40 objective microscopic fields within the hot spot
- Low count not exclude AIP; patchy distribution, evolving fibrosis, previous steroids
- IgG4+/IgG+ ratio of >40%, recommended cut off value
- IgG/IgG4 IHC on biopsy from major papilla  
  Noon et al. Gastrointest Endosc 2010; 71: 900-6

**AIP - frozen section**

**Groove pancreatitis**
- Cystic dystrophy of the duodenal wall / para-ampullary duodenal wall cyst/ cystic dystrophy of heterotopic pancreas/ paraduodenal pancreatitis
- Mass between the head of the pancreas and the second part of the duodenum in pancreatoduodenal groove
- Due to presence of ectopic pancreas in wall of duodenum between ampulla of Vater and minor papilla

**Groove pancreatitis**
- Drainage of pancreatic secretions from ectopic tissue is impaired; duct dilatation, cyst formation and rupture, inflammation
- Chronic alcohol consumption is a further pathogenetic factor, increasing pancreatic secretions in the ectopic pancreas
- Both pathogenetic factors needed; explains rarity of condition, despite ectopic pancreas in duodenal wall being common

**Groove pancreatitis**
- Young to middle-aged male adults with a history of alcohol abuse
- Present with abdominal pain, nausea & vomiting due to duodenal stenosis, weight loss
- EUS – multiple cysts within thickened duodenal wall
- Differential diagnosis – PDAC
- Macroscopy – cystic spaces in thickened duodenal wall and in pancreatoduodenal groove; can extend into pancreas
- Irregular duodenal mucosa with hyperplasia of Brunner’s glands
Groove pancreatitis

Groove pancreatitis

Hereditary chronic pancreatitis

- Described in 1952 as ‘hereditary chronic relapsing pancreatitis’
  (Cerf et al. Gastroenterology 1962; 31: 64-83)
- Rare form of chronic pancreatitis (1-2 % of cases)
- Autosomal dominant, 80% penetrance, variable disease expression
- Initial presentation in children/young adults (<20yrs)
- Recurrent attacks of acute pancreatitis, which progresses to CP in about half of the patients
- Absence of other aetiological factors
- Increased risk of pancreatic cancer
  Otoski et al. Pancreas 2004; 30: 200-4)

Genetics of hereditary pancreatitis

- 1996, gene for HCP mapped to chromosome 7 (7q35)
  (Whitcomb et al. Gastroenterol 1996; 111: 1076-80
  Le Bail et al. Hum Mol Genet 1994; 3: 549-64)
- 1996, Whitcomb et al identified R122H mutation in exon 3 of the protease serine 1 (PRSS1) gene which encodes cationic trypsinogen
- 1997, second mutation (N291 mutation) in PRSS1 gene was discovered
  (Garry et al. Gastroenterol 1997; 113: 1023-8)
- Now >30 mutations in the PRSS1 gene described
- 60-80% of patients with HCP have R122H or N291 gain-of-function mutations

Hereditary chronic pancreatitis

- No mutation been identified in other 20-40% of families
- Mutations in PRSS1 gene are thought to prevent deactivation of inappropriately activated intrapancræatic trypsinogen or to increase trypsinogen activation, resulting in acinar cell autodigestion and subsequent pancreatitis
Diagnostic criteria for HCP

- Exclude other causes of CP in childhood, eg anatomical anomalies, metabolic disorders, cystic fibrosis, trauma, viruses
- Two first-degree relatives, or at least three second-degree relatives, in two or more generations, with recurrent acute pancreatitis and/or chronic pancreatitis, for which there are no precipitating factors
- Detection of p.R122H or p.N29I mutations in the PRSS1 gene is diagnostic

HCP - pathology

- Limited publications
- Dilated pancreatic ducts, protein plugs & calculi, peri-ductal/perilobular fibrosis, pseudocysts
- PanINs
- Normal pancreas
- Extensive fatty infiltration

Histological features of HCP

Liverpool Histology

Histology of HCP

- ‘PRSS1 hereditary pancreatitis is characterized by progressive lipomatous atrophy of the pancreas’ (n=4)
  

HCP – cancer risk

- Cancer risk with chronic inflammatory diseases
- First report of PDAC associated with HCP in 1958
  
  Bartholomew et al. Gastroenterology 1958; 35: 473-7
- Patients with HCP have an estimated 50-fold increased relative risk for developing pancreatic cancer
  
- Develop PDAC at younger age than sporadic patients
- Up to 40% of HCP patients may develop PDAC
- No difference in risk of PDAC based on type of PRSS1 gene mutation
  
  Whitcomb DC. Am J Physiol Gastrointest Liver Physiol 2004; 287: 315-319
  
  Rebourc et al. Gut 2009; 58: 97-103
HCP – cancer risk

- Compare with 2-4 fold increased risk of PDAC with cigarette smoking, 2-20 fold increased risk in chronic alcoholic pancreatitis
- Smoking increases risk of PDAC in HCP, and seems to lower age of onset by nearly two decades
  Lowerfeix et al. JAMA 2001; 386: 169-70
- Avoid alcohol and do not smoke

Pancreatitis

- Chronic pancreatitis – sampling
- Autoimmune pancreatitis – periductal lymphoplasmacytic infiltrate; type 2 not associated with IgG4+ plasma cells
- Groove (or paraduodenal) pancreatitis – localised mass
- Hereditary chronic pancreatitis – PDAC at young age
- Peritumoural pancreatitis