Pathophysiology of Gallstone Formation and Pancreatitis

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Pancreatic secretions and bile are required for digestion

Bile: Emulsification of fat
Pancreatic secretions: Digestion of proteins, carbohydrates and fat

Bile composition

- Secreted by hepatocytes
- Transported through the biliary system
- Stored and concentrated in the gallbladder
- Released into duodenum after ingestion of food (mediated by CCK)

GALLSTONES

Formation and secretion of bile acids

1. Synthesis (0.3-0.6g)
2. Enterohepatic circulation (5-10x daily)

Cholesterol → Cyp7a → Bile acids

Fecal loss 0.3-0.6g (equals hepatic synthesis)
FXR is a bile acid sensor that lowers intracellular bile acid levels (to prevent toxicity).

Cholesterol requires bile salts for solubilization.

Secretion of cholesterol

Excess cholesterol precipitates to form cholesterol crystals and stones.

LXR is a cholesterol sensor that lowers intracellular cholesterol levels.

Composition of Gallbladder bile
**Cholesterol stones:**
- Great majority of all stones in the US (>70%)
- either pure cholesterol stones or mixed stones (more than 50% cholesterol content)

**Pigment stones:**
- contain pigment = bilirubin
- usually due to increased hemolysis
- or due to decreased bilirubin conjugation

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**Factors Favoring Cholesterol Gallstones**

- Hepatic Production of Lithogenic Bile
  A. Decreased Secretion of Bile Acids
     1. Fasting (pooling of bile salts in gallbladder)
     2. Decreased bile salt synthesis despite diminished pool
     3. Cyp7a mutations (rare)
     4. Decreased bile acid return to liver (ileal resection)
  B. Excess cholesterol secretion
     1. Obesity
     2. Estrogens
     3. Genetic factors/Ethnicity (Pimas)

- Gallbladder Factors
  1. Stasis (TPN, progestins, crash diet)
  2. Nucleation (increased mucoproteins)

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**x-Ray Appearance of Gallstones**

<table>
<thead>
<tr>
<th>Radio-opaque</th>
<th>Radioluscent</th>
</tr>
</thead>
<tbody>
<tr>
<td>27% = Cholesterol Stones</td>
<td>83% = Cholesterol Stones</td>
</tr>
<tr>
<td>73% = Pigment Stones</td>
<td>17% = Pigment Stones</td>
</tr>
</tbody>
</table>

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**Natural History of Gallstones**

- 80% of all gallbladder stones will never cause symptoms
- 1-4% of gallbladder stones/year cause symptoms (e.g. colic, pancreatitis)

**Schematic diagram for the management of gallstone disease**

- **Asymptomatic**
  - Galbladder stones
  - Follow-up
- **Symptomatic**
  - Complicated
  - Laparoscopic Cholecystectomy
  - ERCP
- **Uncomplicated**
  - Observation
  - Ursodiol
  - Possibly emergency surgery

Only if contraindications for surgery:
- Observation
- Ursodiol
- Possibly emergency surgery
**PANCREAS PHYSIOLOGY**

**Pancreas macro- and microanatomy**

**Ion Transport in Duct cells**

**Major functional units**

**Bicarbonate secretion is regulated through hormonal and neural mechanisms**
Regulation of Enzyme Secretion

- Cephalic phase: Food cues
- Gastric phase: Distension
- Intestinal phase: CCK-sensing Vagal Afferents

Dorsal Vagal Complex

Vagal Efferents

Ach, VIP, GRP

M3-R

Digestive Enzymes

CCK-sensing Vagal Afferents

Intestinal phase: CCK-IP

Proteins, AA, FA

Classification of pancreatitis

Functional and morphologic changes

- CHRONIC
  - e.g. ETOH, hereditary
  - Outcome: Pain
  - Endocrine insufficiency
  - Exocrine insufficiency

- ACUTE RECURRENT
  - e.g. sludge, SOD
  - Outcome: Recovery or death

- ACUTE
  - e.g. stone, drug, toxin
  - Outcome: Recovery or death

Etiology of Acute Pancreatitis

- Alcoholic
- Idiopathic
- Other

Biliary

- Autoimmune
- Drug-induced
- Iatrogenic
- IBD-related
- Infectious
- Inherited
- Metabolic
- Neoplastic
- Structural
- Toxic
- Traumatic
- Vascular

Activation of pancreatic enzymes in the intestine

Trypsinogen → Trypsin

Chymotrypsinogen → Chymotrypsin

Proelastase

Procarboxypeptidase

Prophospholipase

Procolipase

Trypsin

Chymotrypsin

Elastase

Carboxypeptidase

Phospholipase

Colipase

PATHOGENESIS OF PANCREATITIS

1. Blockage of Secretion
2. Activation of Zymogens in Lysosomes (Cathepsin B)
3. Organelle Damage and Cell Injury by Activated Enzymes
Local effects of inflammation and pancreas injury
- Third space losses
- Fat necrosis
- Pancreatic and peripancreatic necrosis

Etiology of Chronic Pancreatitis
- Alcoholic
- Hereditary pancreatitis
- Hypertriglyceridemia
- Autoimmune
- Fibrocalcific (Tropical)

Cytokines Play an Important Role in Pancreatic Injury
- Insult
- Pancreatic Acinar Cell
- Cytokine production
- Chemoattraction and activation
- Inflammation
- Cell Death

Effects of Chronic Alcohol on the Pancreas
- Calcification
- Fibrosis
- Decreased blood flow
- Direct toxic effects
- Cytotoxic lymphocytes
- Altered protein synthesis

Hereditary Pancreatitis
- Mutations in cationic trypsinogen
- Autosomal dominant
- Incomplete penetrance
- Early onset
- Frequent calcification
- Increased pancreatic cancer
PANCREATITIS
CLINICAL CONSIDERATIONS

LABORATORY DIAGNOSIS

Amylase and Lipase are typically highly elevated

Other causes of hyperamylasemia and hyperlipasemia:

- Parotitis
- Acute cholecystitis
- Acute cholelithiasis
- Acute obstruction of biliary tract
- Acute obstruction of pancreatic duct
- Acute pancreatitis
- Acute hepatitis
- Acute myocardial infarction
- Acute respiratory distress syndrome

IMAGING DIAGNOSIS

- Interstitial pancreatitis
- Necrotizing pancreatitis

Higher rate of complications (bacterial infection, organ failure) and mortality

If CT is performed within 24h of first symptoms, findings may be normal

PROGNOSIS OF ACUTE PANCREATITIS

Ranson’s severity score & mortality

During first 48h:

- Hct decrease > 10%
- BUN increase > 5 mg/dL
- Ca2+ < 8 mg/dL
- PaO2 < 60 mm Hg
- Base deficit > 4 mEq/L
- Negative fluid balance > 4L

Scores: 0-2, 3-5, 6-8, 9-11

Acute Pancreatitis Complications

- Grey-Turner sign
- Obstructing Pseudocyst
- ARDS

Acute Pancreatitis Complications

- Infected Necrosis

Treatment

Antibiotic
PANCREATIC FLUID COLLECTION NOMENCLATURE

- Acute collection
  - A.P./ trauma, <48 hrs, no wall
- Pancr. Necrosis (early)
  - A.P., 1-2 wks>30 % necr., no wall
- Organized necrosis
  - A.P.,>2-4 wks, partially walled necrotic debris & panc.
- Acute pseudocyst
  - A.P.,>4 wks, walled juice
- Chronic pseudocyst
  - C.P., walled juice/"retention"
- Pancreatic abscess
  - A.P./C.P./ trauma, peripanc. collection of pus, no debris

Adapted from Bradley et al Atlanta Symposium, Arch Surg 1993 & Baron et al GIE 2002

Chronic Pancreatitis: Diagnostic tests

- x-ray and fecal fat have a low sensitivity to detect CP!
- Amylase and Lipase are often within the normal range!!

Chronic Pancreatitis: Diagnostic tests

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Functional</th>
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<tr>
<td>ERCP/EUS</td>
<td>Secretin test</td>
</tr>
<tr>
<td>CT Ultrasoundogram</td>
<td>Fecal chymotrypsin Serum trypsinogen</td>
</tr>
<tr>
<td>Abdominal x-ray</td>
<td>Fecal fat Blood glucose</td>
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Chronic Pain is a Common Symptom of Chronic Pancreatitis

Exogenous proteases may decrease CCK release and pain in chronic pancreatitis