Causes of Pancreatitis

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Incidence and costs

10-44/100000 acute pancreatitis/year (case fatality 3-10%)

1.6-14/100000 chronic pancreatitis/year

US$ > 2.2 billion 220,000 admissions in 2003.

Audit by BW/MGH x2.5 increase in radiology costs (2007-2010) with no change in outcomes  
Mortele et al., Radiology 2010 advance on line
Causes of acute pancreatitis

‘GET SMASHED’ – about 15% severe course

- Gall stones (38%)
- Ethanol (35%)
- Trauma (1.5%)
- Steroids
- Mumps
- Autoimmune
- Scorpion venom
- Hyperlipidemia, hypothermia and hypercalcaemia
- ERCP (5%) and emboli
- Drugs
Causes of chronic pancreatitis

‘TIGAR-O’

- Toxic/metabolic (alcohol, smoking, Ca, lipids, CRF, toxins approximately 80%)
- Idiopathic (10-30%; bimodal 20 v 55 years, minimal change, tropical)
- Genetic (CF, AD cationic trypsinogen, AD modifiers CFTR/SPINK, etc)
- Autoimmune (Isolated, syndromic 2-6%)
- Recurrent acute pancreatitis (postnecrotic, vascular diseases, irradiation)
- Obstructive (dominant narrowing of pancreatic duct – trauma, intraductal stones, SOD, pancreas divisum, sequelae of acute pancreatitis)

Alcohol

• No threshold beneath which pancreatitis does not occur
• Risk exponential increase with dose
• 5% of heavy drinkers develop chronic pancreatitis (>80g/day for >10 years)
• Recurrent attacks of acute alcohol-induced pancreatitis precede chronic disease

Virus pancreatitis

- Mumps
- Coxsackie
- CMV
- HSV
- HAV, HBV, HCV
Tobacco

- Independent causative effect
- Odds ratio 7.8 - 17.3
- Increases the risk of developing pancreatic cancer

Drug-induced pancreatitis

• 525 different drugs reported to WHO as suspected to cause pancreatitis
• Generally mild course
• Most single case reports
• A few case-control studies
• Pharmacogenetic risks are unknown
• Pancreatitis must resolve on withdrawal of the drug
Drug-induced pancreatitis -2

- Pediatric or elderly
- Females
- Advanced HIV infection
- Inflammatory bowel disease
Drug-induced pancreatitis -3

Definite Drug reaction
a) reasonable temporal sequence from administration of the drug
b) follows a known response pattern that is
c) confirmed by cessation of the drug (de-challenge)
d) confirmed by reappearance of the symptoms upon repeated exposure to the drug (re-challenge)

Probable Drug reaction
a) reasonable temporal sequence from administration of the drug
b) follows a known response pattern
c) confirmed by de-challenge
d) could not be explained by the known characteristics of the patients clinical state

Possible Drug reaction
a) follows a reasonable temporal sequence from administration of the drug
b) follows a known response pattern
c) but that could have been produced by the patients clinical state or other modes of therapy administered to the patient

List of drugs causing pancreatitis

List of definite and probable drugs causing pancreatitis

<table>
<thead>
<tr>
<th>Probable</th>
<th>Cases</th>
<th>Re-exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>13</td>
<td>1</td>
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<tr>
<td>Asparaginase</td>
<td>177</td>
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<tr>
<td>Azathioprine</td>
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<td>Cimetine</td>
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<tr>
<td>Cisplatin</td>
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<tr>
<td>Cytarabine</td>
<td>26</td>
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<tr>
<td>Didanosine</td>
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<tr>
<td>Enalapril</td>
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<tr>
<td>Erythromycin</td>
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<tr>
<td>Oestrogen</td>
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<tr>
<td>Furosemide</td>
<td>21</td>
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<tr>
<td>Hydrochlorothiazide</td>
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<td>Interferon-ab</td>
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<tr>
<td>Lamivudine</td>
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<tr>
<td>Mercaptopurine</td>
<td>69</td>
<td>10</td>
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<tr>
<td>Mesalamine/Olsalazine</td>
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<td>17</td>
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<td>Methyldopa</td>
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<td>Metronidazole</td>
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<td>Opiates</td>
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<td>Pentamidine</td>
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<td>Pentavalentanti-Monisals</td>
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<td>Phenformin</td>
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<td>Simvastatin</td>
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<td>Steroids</td>
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<tr>
<td>Sulfasalazine</td>
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<td>Sulfmethaxazole/</td>
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<td>Trimethoprim</td>
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<td>Sulindac</td>
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<td>Tetracycline</td>
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<td>Valproic acid</td>
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<table>
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<tr>
<th>Possible</th>
<th>Cases</th>
<th>Re-exposure</th>
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<tr>
<td>Carbamazepine</td>
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<tr>
<td>Cyclophenthiazide</td>
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<tr>
<td>Didanosine</td>
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<td>Enalapril</td>
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<tr>
<td>Famotidine</td>
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<td>0</td>
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<tr>
<td>Mapiroline</td>
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<td>0</td>
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<tr>
<td>Mesalazine</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>25</td>
<td>0</td>
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Autoimmune

- Most late adulthood, but wide age range
- Female:male about 2:1
- Mild pain, jaundice, weight loss
- Typical acute pancreatitis rare
- 60% other autoimmune (rheumatoid arthritis, Sjögren’s syndrome, inflammatory bowel disease, autoimmune hepatitis or primary sclerosing cholangitis).
Autoimmune – diagnostic criteria

- **Histological features Diagnostic:**
  1. Periductal lymphoplasmacytic infiltrate with obliteratorive phlebitis (LPSP) in pancreatic tissue
  2. High (>10 cells/hpf) IgG4 positive cells in the pancreas
  3. Lymphoplasmacytic infiltrate with fibrosis in the pancreas

- **Imaging**
  1. CT/MR: diffusely enlarged gland with delayed enhancement
  2. ERCP/MRCP: Diffusely irregular, attenuated main pancreatic duct

Atypical imaging features: Pancreatitis, focal pancreatic mass, focal pancreatic duct stricture, pancreatic atrophy

- **Serology**
  Elevated serum IgG4 level (can see late elevations)

- **Other organ involvement**
  Persistent distal biliary stricture, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis

- **Steroid therapy**
  Resolution of pancreatic/extrapancreatic manifestation with steroid therapy
Genetic

PRSS1 gain-of-function missense mutation

Trypsinogen autoactivation in the pancreas
- p.R122H
- p.N29I
- p.N29T
- p.D19A
- p.D22G
- p.K23R
- p.A16V (in the presence of CTRC)

PRSS1

Trypsin

Pancreas auto-digestion

CTRC (Trypsin)
- p.R122H
- p.R122C

SPINK1
- p.R122H
- p.R122C
Hereditary pancreatitis mutations in trypsinogen
Genetic

Hereditary pancreatitis mutations in trypsinogen c80% HCP (NB Ca risk)

PRSS1 gain-of-function missense mutation

Degrades trypsinogen and trypsin (c2% CP)

Inhibits trypsin (20% ICP 5% ACP)

CFTR ICP 13-37%
# Workup

## Workup checklist for pancreatitis

<table>
<thead>
<tr>
<th>Onset of symptoms</th>
<th>Yes/No</th>
<th>Date/Time</th>
<th>Dates</th>
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</thead>
<tbody>
<tr>
<td>Previous episodes</td>
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**APACHE II**
http://www.globalrph.com/apacheii.htm

**US Amylase/Lipase**

**MR/CT**

**Electrolytes**

**FBC**

**ALT**

**AST**

**Bilirubin**

**Albumin**

**Clotting**

**CRP**

Peaks >72 hours after symptoms start: >150 mg/dL within 48 hours 80% risk of necrotising disease

**Ca fasting TG**

**ANA**

**RnF**

**IgG isotypes**

<table>
<thead>
<tr>
<th>Drugs list</th>
<th>Drug</th>
<th>Date drug started</th>
<th>Risk drug (Yes/No)</th>
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</table>

## Workup checklist for pancreatitis

<table>
<thead>
<tr>
<th>Other autoimmune conditions</th>
<th>Date diagnosed</th>
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**Alcohol intake**

**Estimated daily intake currently**

<table>
<thead>
<tr>
<th>Units/week</th>
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**Max estimated daily intake 5 -10 years ago**

<table>
<thead>
<tr>
<th>Units/week</th>
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**Smoking history**

<table>
<thead>
<tr>
<th>Pack-years</th>
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**Family history of pancreatitis**

<table>
<thead>
<tr>
<th>Yes/No (if yes pedigree)</th>
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http://dl.dropbox.com/u/4912579/Workup%20for%20pancreatitis.xlsx