Pancreatic and Biliary Tract Disorders: Update 2007

Christian Mathy, MD
Division of Gastroenterology
University of California, San Francisco

What’s New: Pancreaticobiliary Disease 2007

• Majority of new management guidelines, research focused on pancreas over last 1-2 years:
  – Recent practice guidelines on Acute Pancreatitis released by American College of Gastroenterology
  – Extensive work on finding better ways to characterize, risk stratify Pancreatic Cystic Lesions
  – Growing awareness of Autoimmune Pancreatitis as important cause of pancreatic disease
• Thus, this Update talk will mainly focus on Pancreatic Diseases, though with discussion of Manifestations of Gallstone Disease

Pancreatic and Biliary Tract Disorders: Update 2007

• Acute pancreatitis
• Cystic lesions of the pancreas
• Autoimmune pancreatitis
• Gallstones/Choledocholithiasis

Case #1

A 62 yo woman with type II DM is evaluated for abrupt onset nausea, emesis, epigastric pain. Physical exam shows Tmp 38.9 °C, Pulse 115, BP 150/95, icteric sclerae and moderate epigastric TTP though soft.

Labs: WBC 17.2K, HCT 49, AST 224/ALT 210/T Bili 6.0/Alk Phos 365, Na 149, Cr 1.1.

What radiographic test would you order?:

1. Abd plain film
2. Abd ultrasound
3. CT abd with IV contrast
4. CT abd without IV contrast

Acute Pancreatitis

• Three phases can occur in acute pancreatitis:
  1. Premature activation of trypsin within acinar cells, activating other enzymes
  2. Intrapancreatic inflammation
  3. Extrapancreatic inflammation
     – Steps 2 and 3 mediated by activated inflammatory cells and cytokines
• Majority of pancreatitis mild, though in 10-20% progresses to Step 3/systemic inflammatory response syndrome (SIRS)
     – Tachycardia, increased respiratory rate, hypo- or hyper-thermia, leukopenia or leukocytosis
     – Recently described genetic polymorphisms in inflammatory mediators seem to predispose to SIRS
     (Banks et al J Am Coll Intern Med 2006, as well as for following slides on AP)
# Acute Pancreatitis

**In US, approx 210,000 admissions for acute pancreatitis (AP)**

**Typical presentation is abrupt onset epigastric pain that persists for > 24 hrs**

**Diagnosis requires at least 2 of 3 criteria:**
- Abdominal pain characteristic of AP
- Amylase and/or lipase > 3X upper limit of normal
- CT findings characteristic of AP

**Diagnosis allows for minimal amylase/lipase elevations**

- Lipase remains elevated longer than amylase and is preferred serum marker
  - Lipase normal in some conditions that increase amylase (macroamylasemia, some cancers, parotitis, intestinal inflammation)
  - Degree of amylase/lipase elevation not prognostic
  - Daily amylase/lipase measurements of very limited value

**Causes of Acute Pancreatitis:**
- Gallstones/microlithiasis
- Alcohol
  - These two make up vast majority of cases
- Drugs (6MP/Azathioprine, thiazides, OCPs)
- Abdominal trauma
- Post-Endoscopic Retrograde Cholangiopancreatography
- Other: Hypertriglyceridemia, Malignancy
- Idiopathic
  - Mutations in CFTR and trypsinogen genes in some “idiopathic” patients
  - Pts with CFTR mutations and AP very rarely have other manifestations of cystic fibrosis

**Differential diagnosis:**
- PUD, biliary colic, bowel obstruction, mesenteric ischemia, dissecting aortic aneurysm, inferior wall MI

**During initial hospitalization for AP, “reasonable” attempts at determining etiology indicated:**
- Determine history of gallstone or biliary tract disease, alcohol and medication usage, recent trauma, family history of pancreatitis
- In first 24 hrs, blood tests for liver chemistries, triglycerides, calcium
- Abd Ultrasound usually performed to assess for gallstones
- When AP diagnosis in doubt, contrasted CT scan with thin-sections. Role of MRI/MRCP being studied.

**Severe AP:**
- Early signs:
  - Three or more Ransom signs
  - APACHE-II score of 8 or greater
  - Elevated hematocrit > 44 (dehydration)
- Organ failure:
  - Shock, hypoxemia, creatinine > 2 after rehydration, maybe GI bleeding
  - Local complications:
    - Necrosis (> 30% of pancreas nonenhanced on CT scan with contrast, suggested by CRP > 150 at 36-72 hrs)
- Presence of necrosis more serious than abscess or development of pseudocyst
  - 85% pts have interstitial “mild” pancreatitis, 15% necrotizing (54% of these develop organ failure and 33% develop infected necrosis)
  - Overall mortality in AP 5%
  - Mortality without organ failure near 0%
  - With organ failure can approach 50% (3% with single organ failure, 47% with multiorgan)

**Management:**
- Nothing by mouth
- Fluid resuscitation absolutely critical, should start in ED
  - Hypovolemia can allow progression to necrotizing disease and intestinal ischemia, bacterial translocation
  - Follow urine output, and HCT values at 12 and 24 hrs.
  - Lines to monitor central venous pressure rarely required
- Supplemental oxygen
- Pain control (any narcotic is acceptable, including morphine)
- Transfer to step-down bed or ICU if any organ failure, lack of response to fluid resuscitation, significant comorbidities
- Nutritional support
  - Mild pancreatitis: Restart oral intake in 3-7 dys, when abd pain no longer requires IV narcotics
  - Severe pancreatitis: Provide nutritional support when clear that pt will be NPO for more than 1-2 wks
  - Enteral feeding via nasojejunal tube likely favored over TPN, though studies on issue in general poor
  - Enteral feeding stabilizes gut barrier function, avoids complications of TPN
  - Place enteral tube in jejunum to limit pancreatic stimulation, though this can be difficult and can delay start of nutrition
Acute Pancreatitis

Management (cont’d):
• Antibiotic use
  – Mild pancreatitis: No role
  – Severe pancreatitis: Debatable
  – Only multicenter, double-blind, placebo controlled study (using Cipro/Flagyl) found no sign. benefit. Criticized for choice of antibiotics and small sample size (Isenmann et al Gastro 2004)
  – In first several dys, pts often appear septic and reasonable to cover with antibiotics while infection ruled-out
  – In pts with severe pancreatitis, should obtain contrasted CT scan at 48 hrs to assess for necrosis. Scans earlier in course can miss necrosis.
  – If necrosis present, should perform FNA to assess for infection. If infected, start Imipenem. Infection most commonly found in 2nd / 3rd wk of hospitalization
  – Surgical debridement recommended in infected necrosis, or in sterile necrosis that remains symptomatic past 2-3 wks. Even with infected necrosis, growing trend to wait 2-3 wks in “stable” pts to allow for organization of infection

Role of ERCP in pancreatitis
– Indicated for patients with cholangitis, pancreatic ductal disruption (for transpapillary stent placement), persistent choleodocholithiasis
– Timing of ERCP for gallstone pancreatitis without cholangitis debatable
  – Three published randomized/controlled trials to date on early (with 24 hrs) vs delayed ERCP in gallstone pancreatitis (Neoptolemos et al Lancet 1988; Fan et al NEJM 1993; Folsch et al NEJM 1997)
  – Metaanalysis of these trials showed early ERCP with stone extraction/sphincterotomy reduced complications in severe biliary pancreatitis but not mild pancreatitis, no mortality benefit in any group (Ayub et al Cochrane Database Syst Rev 2004)

Complications:
– Pseudocyst
– Hemorrhage
– Pseudoaneurysm
– Thrombosis
– Infection
– Necrosis

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Acute Pancreatitis

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- Thrombosis
- Infection
- Necrosis

Case #2

A 52 yo man without any medical problems underwent a screening virtual (CT) colonography. The colon was normal, though a 4.4 cm cyst without calcification was noted in the pancreatic body within an otherwise normal appearing pancreas, pancreatic duct, and nl biliary system. The pt has no history of pancreatitis, alcohol use, abd trauma, or biliary disease.

What would you do next in his evaluation?:
1. Refer to a pancreatic surgeon for resection
2. Obtain a CT with thin cuts through the pancreas
3. Refer for Endoscopic Ultrasound (EUS)
4. Refer for Endoscopic Retrograde Cholangiopancreatography (ERCP)

Cystic lesions of the pancreas

• >90% pancreatic cysts non-neoplastic
• Most common presentations are with abd pain, weight loss, jaundice, pancreatitis, palpable mass
• Approx 1/3 cysts found incidentally
• Among pts with no symptoms, 17% had malignant cysts and 42% cysts with malignant potential
• 37% cysts diagnosed/managed incorrectly (Warshaw et al Ann Surg 1990)
• Basic issues:
  – Is lesion neoplastic?
  – What is risk of malignant degeneration?

Differential diagnosis:
• Simple (or congenital) cysts
• Pseudocysts
• Serous cystadenomas
• Mucinous cystic neoplasms (mucinous cystadenomas or cystadenocarcinomas)
• Intraductal papillary mucinous neoplasms (IPMN)
• Other: Cystic endocrine tumors, cystic degeneration of adenocarcinomas, pseudopapillary neoplasms
Cystic lesions of the pancreas

- Pseudocysts (inflammatory cysts) are nonneoplastic, make up 90% of all cysts
- Simple cysts 5-10%
- Cystic neoplasms 5-10%
- Most common cystic neoplasms:
  - Serous cystadenomas (32-39%)
  - Mucinous cystic neoplasms (10-45%)
  - Intraductal mucinous neoplasms (21-33%)

(Brugge et al NEJM 2004)

Cystic lesions of the pancreas

Diagnosis:
- Helical CT with contrast, thin sections excellent first test
  - Presence of central scar highly diagnostic of serous cystadenoma
  - Peripheral calcification specific to mucinous neoplasm, predictive of CA
  - Other features overlap, diagnostic value debatable
- Endoscopic ultrasound, with fluid aspiration
  - 1% risk of complications
  - Most predictive feature is cyst CEA (>192 ng/mL), still only 79% accurate.
  - EUS alone fair; cytology poor, 59% accurate
  (Brugge et al Gastro 2004)
- MRI may add some information, PET being studied

Cystic lesions of the pancreas

Treatment:
- Resection advised for symptomatic lesions, mucinous or potentially mucinous lesions
  - Whipple’s resection for lesion in head (2% mortality in expert centers)
  - Distal pancreatectomy for lesions in tail, can save spleen if no CA
  - No need for EUS if asymptomatic
  - ~20% pts with IMPNs require total pancreatectomy due to growth along ducts
- Even with CA present, mucinous cystadenomas 100% cured if no transmural invasion, IPMNs have 50% 5-yr survival with resection
  (Chari et al Gastro 2002)

Cystic pancreatic disease

<table>
<thead>
<tr>
<th>Cystic mass</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudocyst</td>
<td>Common, Hx of pancreatitis</td>
</tr>
<tr>
<td>Serous cystadenoma</td>
<td>Numerous small cysts, central calcification(s)</td>
</tr>
<tr>
<td>Mucinous cystic neoplasm</td>
<td>Few large cysts, rare ductal communication</td>
</tr>
<tr>
<td>Intraductal papillary mucinous neoplasm</td>
<td>Dilated duct, gaping papilla</td>
</tr>
<tr>
<td>Simple cysts / other</td>
<td>Myriad</td>
</tr>
</tbody>
</table>

Treatment (cont’d):

Asymptomatic, CT diagnostic for serum lesion?
- YES: Monitor
- NO: EUS

Diagnostic for serum lesion?
- YES: Monitor
- NO: FNA

Malignant: Surgery
Non-malignant: Monitor
Case #3
A 60 yo man presents with 7 months of mild epigastric pain and 14 lb wt loss. Exam notable for slightly icteric sclerae and mild epigastric tenderness. He had no past medical history, no known exposure to alcohol or drugs. EGD and colonoscopy 2 months ago both normal.

Labs: 6mos prior
- Amylase 176 U/L, Alk Phos 200, T bili 2.2
- CT scan: Enlargement of the pancreatic head and distal body without obvious mass or peripancreatic inflammatory changes, dilated CBD to 1.2 cm.

On presentation
- Amylase 190 U/L, Alk Phos 245, T bili 2.2
- CT scan: Enlargement of the pancreatic head and distal body without obvious mass or peripancreatic inflammatory changes, dilated CBD to 1.2 cm.
- ERCP: Normal papilla, moderate CBD dilation without stones but with narrowing through the pancreatic head, a 2cm long narrowing of the distal PD without upstream ductal dilation. Cytologic brushings negative.

EUS/FNA: Confirmed ERCP findings, as well as noting multiple EUS changes of chronic pancreatitis. FNA X 5 of the enlarged pancreatic head revealed thick bands of collagen with minimal inflammation and no atypical cells.

The most appropriate next step would be:
1. Obtain MRI/MRCP
2. Start treatment with prednisone
3. Start treatment with pancreatic enzyme replacement
4. Referral for exploratory surgery

Autoimmune Pancreatitis:

Autoimmune Pancreatitis: Background
- Chronic pancreatitis (CP) → a chronic inflammatory, fibrotic condition, with loss of pancreatic exocrine and ultimately endocrine function
  - Major cause is alcohol, though also metabolic, genetic and structural/obstructive etiologies
  - Historically, 30% of CP without identified cause, labeled "idiopathic"
  - In last 10-15 yrs, expanding evidence for CP lacking known risk factors but with evidence of an autoimmune process. Termed "Autoimmune Pancreatitis" (AIP) in 1995 (Yoshida et al)
  - Majority of initial AIP reports published from Japan, considered a disease only of this area
  - More recent studies suggest that a substantial percentage of "idiopathic" CP in Western countries also AIP
  - AIP found in 6% of CP patients in Italy, similar to reports from Korea and Japan of approximately 5% (Pearson et al, Kim et al)

Autoimmune Pancreatitis: Presentation and Diagnosis
- Mean age 59; male-to-female ratio 15:2
- Major presenting symptoms are painless jaundice, weight loss, mild mid-abdominal pain (very rare to have severe pain or acute pancreatitis)
- Majority have cholestatic liver tests with normal or mildly elevated amylase/lipase
- ~60% of pts have elevated IgG4 levels, mainly IgG4
- CT scan reveals diffusely enlarged pancreas without peripancreatic inflammatory changes, often with a low-attenuating rim surrounding pancreas. A variant presentation produces only a focal, mass-like enlargement
- ERCP shows pancreatic duct with multiple, segmental strictures with minimal proximal dilation, or irregular diffuse narrowing. In most pts, intrapancreatic portion of bile duct narrowed

Autoimmune Pancreatitis: Pathogenesis
- Considered an autoimmune process:
  - Assoc with hypergammaglobulinemia, lymphoplasmacytic pancreatic infiltrates, coexisting autoimmune diseases (Sjogren’s, primary sclerosing cholangitis [PSC]), and a marked improvement with steroid therapy
  - A CD4+ T-cell mediated reaction identified against carbonic anhydrase II and lactoferrin
  - CA-II and lactoferrin also present in salivary/lacrimal glands and bile ducts, possibly explaining coexistence of AIP with Sjogren’s and PSC

Autoimmune Pancreatitis
Primary differential diagnosis for AIP is “standard” chronic pancreatitis and pancreatic cancer.
- Ways to differentiate:
  - Pancreatogram, radiographic findings (described on next slides)
  - IgG, IgG4 levels
  - Response to steroids, especially response of concurrent biliary obstruction (if present). Evident in 2-4 wks.
  - CA 19-9 levels rarely helpful
  - In pts with mass-like lesions, should exclude whenever possible malignancy by endoscopic ultrasound with FNA or CT-guided percutaneous biopsies
Autoimmune Pancreatitis vs Chronic Pancreatitis

<table>
<thead>
<tr>
<th>Autoimmune Pancreatitis</th>
<th>Alcoholic Chronic Pancreatitis</th>
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<tbody>
<tr>
<td>Direct pancreatogram</td>
<td>Irregular narrowing</td>
</tr>
<tr>
<td></td>
<td>Irregular dilation</td>
</tr>
<tr>
<td>Phlegmon/pseudocyst</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Calcification or stone</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Pancreatic parenchyma</td>
<td>Enlargement</td>
</tr>
<tr>
<td></td>
<td>Atrophy</td>
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</tbody>
</table>

Autoimmune Pancreatitis vs Pancreatic Cancer

<table>
<thead>
<tr>
<th>Complete PD cutoff</th>
<th>Uncommon</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal stricture</td>
<td>Multiple</td>
<td>Localized/single</td>
</tr>
<tr>
<td>Upstream duct dilation</td>
<td>Mild</td>
<td>Marked</td>
</tr>
<tr>
<td>Duct evident in mass</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Diffuse pancreatic swelling</td>
<td>Very frequent</td>
<td>Rare</td>
</tr>
<tr>
<td>Double duct sign</td>
<td>Common</td>
<td>Common</td>
</tr>
</tbody>
</table>

Autoimmune Pancreatitis: Treatment

- Steroids, steroids, steroids
- Detailed steroid schedule not established, but my practice (following expert consensus):
  - Prednisone 40 mg/dy for 4-6 wks (until symptoms resolution)
  - Subsequent taper by 5mg/wk every 3 wks to off
  - Some continue low-dose pred at 5-10 mg/dy, though I do not unless forced by relapse
- Response to treatment dramatic, with concurrent CT, pancreatogram, and symptomatic improvements all often seen in 2-4 wks. IgG levels also normalize.
- Biliary obstruction usually resolves during treatment
  - Marked contrast to recalcitrant biliary obstruction seen with standard chronic pancreatitis
  - Often able to remove biliary stent (if it had been needed for biliary obstruction) by 2-3 months

Autoimmune Pancreatitis: Relapse

- Long-term prognosis not well described
- In a study of 23 pts with AIP followed for mean 4.5 yrs, only 1 of 23 pts had relapse (Horiuchi et al. GIE 2002)
- Relapses seem to respond as well to prednisone course as with original flare, though would then maintain on low dose prednisone (5-10/dy)
- Use of immunomodulators (methotrexate, MMF) for maintenance of remission not yet adequately evaluated
- Risk for subsequent development of pancreatic adenoCA not well-studied

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- Gallstones/Choledocholithiasis

Gallstones/Choledocholithiasis

Bile:
- Composed of water, inorganic solutes, organic solutes (bilirubin, bile acids, biliary lipids)
  - Bilirubin is degradation product of heme
  - Bile acids are bipolar molecules synthesized from cholesterol
    - Primary bile acids: cholic and chenodeoxycholic acid
    - Secondary bile acids: deoxycholic and lithocholic acid, converted from primary acids by gut bacteria
  - Gallbladder concentrates bile 10 fold during fasting
  - Main function of bile is to facilitate fat digestion/absorption
  - 90% of bile is reabsorbed in terminal ileum and returned to liver via portal system, with 4-12 cycles per day (Enterohepatic Circulation)
Gallstones/Choledocholithiasis

• Stone formation requires:
  – Cholesterol supersaturation
    • From deficient bile acid secretion (due to reduced EHH, cholesterol synthesis as occurs with age/liver dz); or
    • From cholesterol supersecretion (due to hormonal stimuli, obesity, age, hyperlipidemia)
  – Crystal nucleation (occurs in supersaturated environment)
  – Gallbladder hypomotility (due to supersaturated bile itself, pregnancy, prolonged TPN)
• Gallbladder stones:
  – In the West, present in 10-20% woman, 5-10% men
  – Predominantly cholesterol in 80% pts, bilirubin pigment in 20% pts

Types of Stones:
• Cholesterol stones
  – Composed of cholesterol crystals, calcium, bilirubin
  – Usually firm but not hard, yellow-white/green
• Black pigment stones
  – Oxidizes in GB, made of dense calcium bilirubinate and often related to infection
  – Occur with older age, cirrhosis, hemolysis, idiopathic
• Brown pigment stones
  – Originates in bile ducts, made of calcium bilirubinate plus ~30% cholesterol (softest of the stones)
  – Occur with bile stasis and bacterial colonization

Gallstones/Choledocholithiasis

Manifestations of Gallstones
• Asymptomatic gallstones
  – By 50 yrs, 15-20% pts will develop biliary colic, and 2-3% pts develop biliary complications (though rarely always preceded by colic)
• Biliary colic
  – 90% pts will have recurrent colic, 1-2% pts/year develop biliary complications
• Cholecystitis
  – Bacterial in 40–50% pts
• Cholangitis
  – Cholecystitis in 70% pts; multiple organisms in blood cxs in ~50% pts
• Choledocholithiasis
• Gallstone/biliary pancreatitis
• Recurrent pyogenic cholangitis
  – Most common in East Asian pts
  – Patients with recurrent biliary cholangitis, intrahepatic pigment stones, and biliary strictures (mainly in the left ductal system)
  – May be result of biliary pyogenic infection, malnourished diets high in carbohydrates, and/or sphincter of Oddi dysfunction

Risk of choledocholithiasis

In patients with symptomatic cholelithiasis:

High risk
• Bilirubin > 2 mg/dL, Alkaline phosphatase > 150 mg/dL
• Cholangitis, jaundice
• CBD diameter > 10 mm, visualized CBD stone
• Risk of CBD stones: 50-80% (Use ERCP)

Intermediate risk
• Bilirubin 1.5–2.0 mg/dL, Alkaline phosphatase 110–150 mg/dL
• Remote jaundice, pancreatitis
• CBD diameter 8-10 mm
• Risk of CBD stones: 20-50% (Use EUS, Intra-op cholangiography [IOC], MRCP)

Low risk
• Normal liver function test results
• CBD diameter 7 mm or less
• No jaundice/pancreatitis
• Risk of CBD stones: 2-3% (No ERCP, no IOC, no MRCP)

**Approximately 1/3 of pts with CBD stones spontaneously pass them by 72 hours

Pancreatic and Biliary Tract Disorders: Update 2007

• Acute pancreatitis
• Cystic lesions of the pancreas
• Autoimmune pancreatitis
• Gallstones/Choledocholithiasis

Case #4

• A 42 yo man presents with symptomatic gallstone disease, following two similar episodes over the past few months.
  – He is afebrile. His laboratory tests are notable for a normal WBC, AST 38, ALT 45, Alk Phos 145 (nl < 110), tBili 1.8 (nl < 1.5), amylase 30.
  – A transabdominal U/S shows stones in the GB and mild dilation of the CBD to 8 mm but without CBD stones visualized

What options are available to exclude a CBD stone?
What is the most cost-effective approach to excluding a CBD stone in this patient?
Thanks to Benjamin Yeh, MD, from UCSF Abdominal Imaging section for providing several radiographic images