Management Issues in Chronic Pancreatitis

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25 year old female “Small-duct” Chronic Pancreatitis

- Cambridge I-II imaging criteria (main duct normal)
- Recurrent abdominal pain
- Fluctuating pancreas enzymes
- Chronic Abdominal Pain
19 year male old “Big-duct” Chronic Pancreatitis

- Cambridge III-IV imaging criteria (main duct involvement)
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Outline

- Diagnosis
- Exocrine Insufficiency
- Metabolic Bone disease
- Pain Management
- Pancreas Cancer
- Autoimmune Pancreatitis
Pancreatic Center of Excellence
Diagnostic Tests Options

• Definitive Diagnosis
  – Patient profile + TiGAR-O Risk factors + Imaging + Physiology
  – Diagnosis in patients with Cambridge I / II criteria (side branch changes, no main duct involvement) challenging

• Radiology / Imaging
  – CT Pancreas protocol
  – MRI/sMRCP/DW MRI
  – Cambridge III / IV criteria (main duct involvement)

• Advanced Endoscopy
  – EUS +/- PFT [30 min screen]
  – ERCP
  – EUS score >= 5
  – Cambridge III / IV criteria (main duct involvement)

• Biochemical / Lab evaluation
  – CBC, CMP, Fecal elastase, serum trypsin

• Pancreas Function Testing
  – Endoscopic / Dreiling Pancreas Function Test (ePFT): 30 min screen; 1 hour diagnostic
  – PFT peak bicarbonate > 75 (NPV 97%, PPV 45%)

Chronic Pancreatitis: CT Scan
finding urinary markers for chronic pancreatitis

Discovery

![Graph showing max normalized SC for Peptidases, Amylases, Lipases, Ig]

- * p value < 0.05
- ** p value < 0.005

finding urinary markers for chronic pancreatitis

Discovery

blue: specific for E (equivocal/mild)
red: specific for M (moderate/severe)
green: gradual increase

Indirect Tests for Exocrine Function

- Sudan stain
  - Qualitative fecal fat
  - Fat droplets
- Pancreatic elastase 1
  >201 Normal
  100-200 Mild
  <100 Severe

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic Elastase 1</td>
<td>80 mcg/g</td>
<td>≥ 251 mcg/g</td>
</tr>
</tbody>
</table>

Positive    Negative
Measuring Exocrine Function in Adults: Why?

- Recognition of exocrine insufficiency
  - Maldigestion associated morbidity / mortality

- Malabsorption of fat-soluble vitamin
  - *Pancreatology* 2008; 8:583-6
    - Vitamin D
    - Osteopathy associated
    - Bone fractures associated with low fecal elastase-1
    - Vitamin A - Night blindness, visual impairment
    - Vitamin E - Neurologic symptoms
    - Vitamin K - Coagulopathy

Inflammation Induces an Imbalance between Osteoclast and Osteoblast Activity

High Prevalence of Low-Trauma Fracture in Chronic Pancreatitis

April S. Tignor, MD, MPH, Beichen U. Wu, MD, MPH, Tom L. Whitlock, MD, MPH, Rocio Lopez, Kathryn Repas, Peter A. Banks, MD and Darwin Conwell, MD

OBJECTIVES: Chronic pancreatitis (CP) is associated with risk factors that may negatively impact bone and mineral metabolism. The important clinical endpoint of osteoporosis is “low-trauma” fracture. The purpose of this study was to examine the prevalence of “low-trauma” fracture in patients with CP, compared with fracture rates in “high-risk” gastrointestinal (GI) illnesses, for which metabolic bone disease screening guidelines are in place.

METHODS: This is a retrospective cohort database study examining patients with CP and “high-risk” GI illnesses seen at a single tertiary care center. Time points ranged between 31 July 1996 and 31 July 2008. The main outcome measure was “low-trauma” fracture prevalence using specific International Classification of Diseases, Ninth Revision, Clinical Modification fracture codes.

RESULTS: A total of 3,192 CP patients and 1,461,207 non-CP patients were included in the study. The fracture prevalence (patients with fracture per total patients) was as follows: controls, 1.1% (16,208/1,436,699); Crohn’s disease, 3.0% (182/6057); CP, 4.8% (154/3192); celiac disease, 4.8% (908/16,148); Crohn’s disease, 3.0% (797/26,000); and pre-diabetes, 3.0% (797/26,000). Prevalence for each group was statistically greater than controls (P<0.001). CP fracture prevalence was greater than controls (P<0.001) and Crohn’s disease (P<0.001), and comparable with the remaining “high-risk” GI illness groups (P>0.05). The odds of fracture (odds ratio (OR), 95% confidence interval (CI)) compared with controls, adjusted for age, gender, and race was CP 2.4 (2.1, 2.9); Crohn’s disease 1.7 (1.5, 2.0); gastritis/cancer 2.5 (1.5, 4.1); celiac disease 2.6 (2.4, 2.7); and celiac disease 2.7 (2.1, 3.4). The odds of fracture for each disease group were statistically greater than controls (P<0.0001).

CONCLUSIONS: The prevalence of low-trauma fracture in CP patients is comparable with or higher than that of “high-risk” GI illnesses, for which osteoporosis screening guidelines exist.

Increased Bone Turnover markers in Chronic Pancreatitis

Duggan, SN et al., Am J Gastro 2015
Enzyme Replacement Therapy

### Algorithm Exocrine Insufficiency

- **Dose adjustment**
  - 40 – 80,000 IU / meal
- **Enteric coated**
  - Protects enzymes
  - Rx: steatorrhea
- **Acid suppression**
- **Acid neutralization**
  - Lipase protection
- **New Drugs**
  - NDA and FDA
  - Standardization

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**Table 2. Pancreatic Enzyme Products**

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Manufacturer</th>
<th>Lipase content (USP)/pill or capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zenepep</td>
<td>Enteric-coated porcine</td>
<td>Apatalis</td>
<td>3000, 5000, 10,000, 15,000, 20,000</td>
</tr>
<tr>
<td>Creon</td>
<td>Enteric-coated porcine</td>
<td>Abbott</td>
<td>3000, 6000, 12,000, 24,000</td>
</tr>
<tr>
<td>Pancrease</td>
<td>Enteric-coated porcine mixed with bicarbonate</td>
<td>OrthoMcNeil-Jansen</td>
<td>4200, 10,500, 16,800, 21,000</td>
</tr>
<tr>
<td>Pertzye</td>
<td>Enteric-coated porcine</td>
<td>Digestive Care</td>
<td>8000, 16,000</td>
</tr>
<tr>
<td>Uthesa</td>
<td>Enteric-coated porcine</td>
<td>Apatalis</td>
<td>13,800, 20,700, 23,000</td>
</tr>
<tr>
<td>Viskace</td>
<td>Tablet non-enteric-coated porcine</td>
<td>Apatalis</td>
<td>10,440, 20,880</td>
</tr>
</tbody>
</table>

Forsmark, C Gastroenterology 2013

Pezzilli, R et al., World Journal Gastro 2013
Chronic pancreatic pain is a complex, multi-level Neuropathic pain syndrome
Demir et al., Langenbecks Arch Surg 2011

- Cerebral cortex - Level 3
  - Cortical reorganization
  - Central sensitization
    - Hyperalgesia
    - Allodynia

- Spinal / Peripheral - Level 2
  - DRG and spinal cord hypersensitivity

- Intrapancreatic - Level 1
  - Neuropathic mechanisms
  - Nociception

There is Pain-Associated Adaptive Cortical Reorganization in Chronic Pancreatitis

Healthy

Chronic Pancreatitis

CP subjects respond differently to painful electrical stimulation of the sigmoid

Olesen, SS et al., Pancreatology, 2011
Non-Surgical Options for Pain Control

- **Lifestyle modification**
  - Alcohol abstinence
  - Smoking cessation

- **Non-narcotic Management**
  - Adjunctive agents
    - Pregabalin
  - Antioxidants
    - Patient population specific
  - Tramadol
  - Uncoated PERT
  - Pancreatic rest
    - NJ feeding or TPN

- **Narcotic analgesics**
  - Pain Therapy Consultation: psychology, anesthesia, chemical dependancy
  - Detox / wean narcotic dose

Medical Evidence:
- Nordback I, Gastroenterology 2009
- Yadav D, Arch Intern Med 2009
- Olesen SS, Gastroenterology 2011
- Bouwenese SH, Plos One 2012
- Bhardwaj P, Gastroenterology 2009
- Dhingra R, Pancreas 2013
- Wilder-Smith CH et al., Dig Dis Sci 1999
- Slaff J, Gastroenterology 1984
- Isaksson G, Dig Dis Sci 1983
- Stanza G, et al., JPEN 2005

19 year male old “Big-duct” Chronic Pancreatitis

- Cambridge III-IV imaging criteria (main duct involvement)
- Recurrent abdominal pain
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- Chronic Abdominal Pain
Endoscopic therapy:
*EHL, ESWL, CPB*

Surgical Therapy:
*Drainage versus Resection procedure*
140 eligible patients
72 randomized to surgical vs. endoscopic therapy

Surgery
• 80% resection / 20% drainage

Endotherapy:
• 100% Sphincterotomy/Stent
• 23% with stone removal

Conclusion:
Endotherapy > Surgery
Short term relief (1 year)
51.6 versus 42.1% complete relief

Surgery > Endotherapy
Long term pain relief (5 year)
36.9 versus 14.3% complete relief


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EUS Guided Celiac Plexus Block:

**Block the Pancreatic Nerves**

<table>
<thead>
<tr>
<th>Study</th>
<th>Pain Relief Reported Out of Total Patient</th>
<th>Observed Proportion</th>
<th>Analysis for Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grass et al.</td>
<td>5/10</td>
<td>0.5</td>
<td>0.5029</td>
</tr>
<tr>
<td>Gross et al.</td>
<td>50/90</td>
<td>0.55</td>
<td>0.5534</td>
</tr>
<tr>
<td>Levy et al.</td>
<td>5/13</td>
<td>0.39</td>
<td>0.4112</td>
</tr>
<tr>
<td>O'Toole et al.</td>
<td>20/31</td>
<td>0.65</td>
<td>0.6312</td>
</tr>
<tr>
<td>LeBlanc et al.</td>
<td>27/51</td>
<td>0.53</td>
<td>0.5044</td>
</tr>
<tr>
<td>Stevens et al.</td>
<td>16/26</td>
<td>0.62</td>
<td>0.6033</td>
</tr>
<tr>
<td>Over All Studies</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

P value for heterogeneity = 0.687.

CI indicates confidence interval; EUS, endoscopic ultrasound.

50% response; short term benefit

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**Total Pancreatectomy With and Without Islet Cell Transplantation for Chronic Pancreatitis**

A Series of 85 Consecutive Patients

Giuseppe Garcea, MD, MRCS, James Weaver, MBChB, John Phillips, MBChB, Cristina A. Pollard, BA, Severine C. Ilten, PhD, M Bala A. Webb, BSc, David P. Berry, MD, FRCS, and Ashley R. Dennison, MD, FRCS

**Remove the Pancreatic Nerves**

Narcotic Use:
- 90% initial
- 40% 1 year
- 15% 5 year

(Pancreas 2009;38: 1Y7)
Pain Management

- Smoking, alcohol cessation
- Pancreatic Enzyme Replacement Therapy
  - Inhibits CCK-RF stimulation (trypsin)
  - Small duct disease
- Antioxidant Trial
- Tramadol
- Pregabalin

- Pancreatic Rest
- Pain Characterization
  - Quantitative sensory testing
  - Nerve blockade (CPB or DNB)

- Duct morphology
- Surgical Therapy
  - Large duct
- Total Pancreatectomy with Islet cell transplantation
  - Small duct
- More RCTs greatly needed
  - XRT, RFA, SCS, Secretin
  - Molecular targeted therapy – TRPV1, NGFs, Mast cells

Stevens T, www.clevelandmed.com
CT Scan: Pancreas Adenocarcinoma

CT Report 2007

- The pancreatic duct is diffusely dilated up to 13mm in the head to the level of coarse calcifications in the head.

- There are additional coarse calcifications within the pancreas and within the pancreatic duct in the upstream pancreas.

- IMPRESSION: 1. Findings consistent with chronic pancreatitis with no evidence of acute pancreatitis.

Pancreatitis and Pancreas Cancer: Meta-analysis

Fig. 1. Study-specific and summary risk estimates with 95% Confidence Intervals for the association between different types of pancreatitis and pancreatic cancer risk.
Cumulative Incidence of Pancreatic Cancer is elevated in Chronic Pancreatitis

- **Approx 1% every 5 years**
  - 4-5% at 20 years
- No screening guidelines
- Better methods needed
- Modify Risk Factors: inflammation, alcohol, SMOKING

Histology: Lymphoplasmacytic Infiltrate
Pancreas biopsy
Plasma Cells and Lymphocytes

Is a 2-week steroid trial after initial negative investigation for malignancy useful in differentiating autoimmune pancreatitis from pancreatic cancer? A prospective outcome study
S-H Moon, M-H Kim, D H Park, C Y Hwang, S J Park, S S Lee, D W Seo and S K Lee

Gut 2008;57;1704-1712; originally published online 26 Jun 2008; doi:10.1136/gut.2008.150979
Clinical and surgical outcome: Autoimmune pancreatitis

Assessment of steroid responsiveness (2 weeks after the initiation of steroid trial)

Positive (n = 15)
- Complete clinical remission with further steroid trial (n = 15)
- Long-term follow-up: 27 months (median)
  - Confirmed as AIP without surgical exploration (n = 15)
  - Occurrence of malignancy (n = 0)

Negative (n = 7)
- Surgical exploration (n = 6)
- Refusal of surgery (n = 1)
  - 7 months later
- Pancreatic cancer; completely resected (5/6)
- Pancreatic cancer with liver metastasis

Autoimmune: Responsive to steroids
Pancreas Carcinoma: Unresponsive to Steroids

Autoimmune Pancreatitis: Treatment

- Initial: Prednisone
  - 40-60 mg x 4 weeks
  - taper 5 mg/week

- 1\textsuperscript{st} Relapse: Prednisone

- Maintenance prednisone 5-10 mg

- Recurrent relapses
  - \textit{Refer to Pancreas Center of Excellence}
  - Steroid sparing immunomodulators
    - Azathioprine
    - Methotrexate
    - Rituximab
Medical Therapy

- Measure pain severity, character, and impact on QOL
- Refer for formal structured smoking and alcohol cessation programs
- Counsel on good nutrition and initiate supplementation with vitamin D and calcium
  - Baseline bone mineral density testing
- Provide information on local and national support groups
- Initiate analgesics (starting with Tramadol)
  - Increase dose and potency slowly as required
- Initiate adjunctive agents in those with persistent pain or requiring higher dosages or potency of narcotics
  - Pregabalin, Gabapentin
  - SSRI
  - SSNRI
  - Tricyclic antidepressants
- Assess for evidence of coexistent exocrine or endocrine insufficiency and treat if present
  - Fecal elastase or serum trypsin
  - HbA1C or GTT
- Initiate steroids if autoimmune pancreatitis

Surgical Therapy

Assess anatomy of pancreas and pancreatic duct

- Inflammatory mass in pancreatic head
  - With or without dilated pancreatic duct
  - With or without duodenal or biliary obstruction

- Dilated pancreatic duct (ca) (fist)

- Small duct disease (pancreatic duct < 5mm)

- Discuss options with patient, including that data supports superiority of surgery. Surgery remains an option for failure of endoscopic therapy
  - Endoscopic therapy
    - Pancreatic and biliary sphincterotomy
    - Stenture dilation and stenting
    - Lithotripsy
    - Stone extraction
    - Surgical therapy
    - Modified Puestow
  - Continued medical therapy
  - Surgical therapy
    - "Hi-pairy"
    - Total pancreatectomy, with islet cell autotransplantation
Conclusion

• Diagnosis
  – Challenging in Cambridge I-II imaging
  – Diagnostic biomarkers under investigation

• Exocrine Insufficiency
  – Large dosages of enzymes
  – Gastric Acid [PPI; bicarbonate neutralization]

• Metabolic Bone disease
  – DEXA Scan
  – Bone turnover markers elevated

Conclusion

• Pain Management
  – Patient selection
  – Endoscopy
  – Surgery – drainage, resection, TPIAT

• Pancreas Cancer
  – “mimicks” – CP and AIP
  – Biomarker is needed
  – 2 week steroid trial with close follow-up

• Autoimmune Pancreatitis
  – Steroid responsive
  – Referral to PCOE for relapses