Diagnosis and Management of Chronic Pancreatitis

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CP  Evidence based

- APA Practice guideline in CP / Diagnostic\(^1\)
  - 1\(^{st}\) US guideline; part 1 of three; 2014
- PancreasFest
  - Multidisciplinary meeting – multiple annual
    - Address numerous topics to identify current knowledge, gaps and best practice recommendations
- Literature review / multicenter trial data

GOALS

- Update new epidemiologic factors in CP
- Review pathophysiology and new paradigms
- Review diagnostic testing
- Review treatment strategies

Chronic pancreatitis

- Chronic inflammation and glandular damage, leading to the clinical symptoms and findings of CP
- “CP SYNDROME”

**CP / Epidemiology**

- **DEMOGRAPHICS**
  - Men 2x more than women
  - 200K in US have CP; 5-12/100K incidence annually
  - 19K admissions, LOS 5.1 D, $29K charges
  - QOL Quality of life in CP

  \*WORSE than diabetes mellitus, hypertension, rheumatoid arthritis\*


**CP/ Etiology/ TIGAR-O**

- **Toxic/metabolic**
  - Alcohol, Tobacco smoking, hypercalcemia, hyperlipidemia, chronic renal failure, toxins
- **Idiopathic**
  - Early, Late, Tropical
- **Genetic**
  - PRSS1, CFTR, SPINK1, and others.
- **Autoimmune**
  - Isolated, Syndromic
- **RAP/SAPE associated**
  - Post necrotic, vascular, post-irradiation
- **Obstructive**
  - Pancreas Divisum, SOD, duct obstruction
CP / Alcohol

• In past felt to be 70% related to etiology
• NOW appears to be actually about 45% in the US
  – Better classification TIGAR-O
    • Incorporate 1 or more risk factors
  – Cooperative studies advancing understanding of the epidemiology (NAPS)

CP / Alcohol

• Pancreatitis more prevalent in alcoholism
• Absolute risk of pancreatitis heavy drinkers 2.5-3%
• Threshold of 4-5 drinks /day increases risk of CP¹
• Disease modifier
  – Injury to pancreas
  – Modifies the immune response

**CP / Smoking**

Risk ratio increases

NS > 1PPD >> over 1PPD

3x more likely to develop CP

Continued smoking increases risk of disease progression

Stop smoking reduces risk of CP by 50%


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**CP / ETOH / Smoking**

- APA Guideline Take home:

  “Alcohol and smoking are independent risk factors for CP. BOTH are associated with disease progression, and their risks are likely additive”
CP / Genetics

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene Name</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRSS1</td>
<td>Cationic trypsinogen</td>
<td>Increased trypsinogen activation, decreased trypsin degradation</td>
</tr>
<tr>
<td>SPINK1</td>
<td>Pancreatic secretory trypsin inhibitor</td>
<td>Failure of trypsin degradation</td>
</tr>
<tr>
<td>CTRC</td>
<td>Chymotrypsin C</td>
<td>Failure of trypsin degradation</td>
</tr>
<tr>
<td>CASR</td>
<td>Calcium sensing receptor</td>
<td>Increased extracellular ionized calcium; increased trypsin activation and failed trypsin degradation</td>
</tr>
<tr>
<td>CFTR</td>
<td>Cystic fibrosis transmembrane conductance receptor</td>
<td>Impaired flushing of pancreatic ducts leading to trypsin activation</td>
</tr>
</tbody>
</table>

Hereditary pancreatitis


CP / Genetic

- Variable penetrance
- Small proportion of CP with known genetic variants
- Understanding can lead to "personalized medicine"

APA Guideline Take Home
  - "Genetic discoveries are rapidly uncovering new susceptibility factors. Knowledge of gene and gene-,environment interactions may translate into new diagnostic and treatment paradigms"
CP / Autoimmune

<table>
<thead>
<tr>
<th>Feature</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60 ± 15 yrs</td>
<td>48 ± 19 yrs</td>
</tr>
<tr>
<td>Elevate Ig4</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Other organs</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>IBD associated</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Relapse Common</td>
<td>Y</td>
<td>N</td>
</tr>
</tbody>
</table>

LPSP: lymphoplasmocytic sclerosing  
IDCP: idiopathic duct centric

- Mass in the HOP, generalized edema with “halo” sign or sausage like
- Steroid responsive, relapse common in Type 1
- Must Differentiate from pancreatic cancer

Sah RP, Chari ST et al. Differences in clinical profile and relapse rate of type 1 verses type 2 Autoimmune pancreatitis; Gastroenterology 2010;139(1):140-148.

CP / Epidemiology / Race

<table>
<thead>
<tr>
<th>N (%)</th>
<th>NAPS2</th>
<th>NAPS2-CV</th>
<th>NAPS2-AA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>13</td>
<td>8</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>458 (85)</td>
<td>453 (87)</td>
<td>0 (0)</td>
<td>911 (76)</td>
</tr>
<tr>
<td>Black</td>
<td>58 (11)</td>
<td>56 (11)</td>
<td>134 (100)</td>
<td>248 (21)</td>
</tr>
<tr>
<td>Others</td>
<td>23 (4)</td>
<td>12 (2)</td>
<td>0 (0)</td>
<td>35 (1)</td>
</tr>
</tbody>
</table>

Wilcox CM et al. Racial Differences in the Clinical profile, Causes and Outcome of Chronic Pancreatitis. Submitted 2016

• NAPS2 Data set
• 248 B  911 W
Race 2

TIGAR-O Factors N (%)  Black (N=248)  White (N=911)

**Toxic-Metabolic**
- Alcohol*: 198 (79.8)  401 (44.0)
- Tobacco*: 182 (73.4)  305 (33.4)
- Hyperlipidemia: 18 (7.3)  58 (6.4)
- Hypercalcemia: 6 (2.4)  8 (0.9)
- Medications: 6 (2.4)  24 (2.6)
- Chronic Renal Failure*: 8 (3.2)  11 (1.2)
- Toxins*: 2 (0.8)  0 (0.0)
- Idiopathic*: 37 (14.9)  345 (37.9)

**Genetic**
- 6 (2.4)  93 (10.2)

**Autoimmune**
- Autoimmune Pancreatitis*: 0 (0.0)  27 (3.0)
- Autoimmune-associated diseases: 2 (0.8)  27 (3.0)

**Obstructive**
- Pancreas divisum*: 25 (10.1)  189 (20.8)
- Sphincter of Oddi*: 12 (4.8)  93 (10.2)
- Post-trauma stricture: 4 (1.6)  52 (5.7)
- Duct obstruction*: 6 (2.4)  51 (5.6)
- Others (CV/AA only): 5 (2.0)  24 (2.6)
- Miscellaneous (CV/AA only): 19 (10.0)  46 (5.1)

**Miscellaneous (CV/AA only)**

ETOH 80% Vs 44%
Smoke 73 Vs 43%

CP / Race

**Take Home:**
- As compared to whites, blacks were almost twice as likely to have alcohol as a cause of disease.
- Advanced morphological abnormalities were significantly more likely in blacks.
- Abdominal pain was more common, more severe, and more likely to result in disability in blacks.
CP / Pathophysiology

• 2 hit hypothesis model
  – SAPE: sentinel AP event; initiate inflammatory cascade
    • Risk factors previously noted
  – Second episode of AP or oxidative stress
    • Fibrosis, ductal and parenchymal changes
  – 10% of single AP and 36% RAP progress to CP*

*Sankaran S et al. Frequency and progression from AP to CP and risk factors: A meta-analysis. Gastroenterology 2015; 149:1490-1500

Pancreatic stellate cell

• Complex nature and interactions
• Inflammatory infiltrate variable
• Acinar loss – PEI
• Islet loss – pancreatic diabetes

CP/ Pathophysiology

- APA Guide Take home:
  - CP is characterized by fibrosis and atrophy with or w/o chronic inflammation
  - May be focal, patchy or diffuse
  - Progressive disease may lead to EXOCRINE or ENDOCRINE (Type 3c pancreatic diabetes) deficiency
  - Autoimmune CP can mimic pancreatic cancer

CP / Diagnosis

- Based on local expertise
- All recs in relation to appropriate Hx / patient
- No gold standard test for CP syndrome
  - Structure, function and access risk
CP/Diagnosis/ CT

- APA guideline: CT
  - Best for late findings of CP, limited for early
  - Ductal calcifications most specific reliable finding for CP
  - Help in diagnose complications of CP
  - Eval other causes of abd pain

CP/Diagnosis/ MRI: MRCP

- APA guideline: MRI
  - MRI is more sensitive imaging tool for diagnosis of CP
    - Can pick up parenchymal changes before ductal changes (Signal intensity and delayed enhancement)
  - Ductal changes specific and reliable (Cambridge)
  - Stimulation MRI with secretin may improve diagnostic accuracy – ductal and parenchymal
    - Need for EUS like MRI post secretin staging system...
CP / Diagnosis / ERCP

- APA Guideline: ERCP
  - ERCP rarely used for Dx of CP
    - Therapy predominant
  - Correlation of Cambridge criteria and histo is in advanced disease
  - Confounders limits interpretation of ductal changes
    - IOA, age related, post-AP changes, PanIN branch duct changes

CP / Diagnosis / EUS

- APA Guideline: EUS
  - Ideal threshold number of EUS criteria to Dx CP not firmly established
    - >5 or <2 strongly suggests or refutes CP Dx
    - Rosemont Classification
  - EUS features of CP are not necessarily pathologic
    - Aging, normal variant, non pathologic fibrosis (alcoholism, male, obese, smokers...)
  - Poor IOA for EUS CP features limits accuracy and utility of EUS for Dx of CP
    - Early disease
EUS / Elastography

- Hue histogram
  - Qualitative
- Calculated strain ratio
  - Abnormal Vs normal unrelated tissue
  - Compared to Rosemont and numerical


CP / Diagnosis / iPFT

- Indirect PFT – trypsinogen, FPE1, fecal fat, steatocrit
- APA Guideline: iPFT
  - Sensitive for steatorrhea/exocrine dysfunction
  - Moderate sensitive for Dx of severe CP
  - FPE; polyclonal better, effected by watery stool or small bowel disease
  - Fecal chymotrypsin helpful in detecting compliance with PERT

* Imaging to rule out pancreatic CA *
CP /Diagnosis / PFT

- Direct PFT - secretin PFT, CCK PFT, ePFT
  - Peak bicarbonate ≈ histology
- APA Guideline:
  - High sensitivity for late CP; lower for early
  - Traditional oroduodenal tube test accurate but not widely used
  - ePFT correlates well with the traditional testing
    - Conwell DL Cleveland Clinic

CP Diagnosis APA Guide Summary

- When CP Dx criteria met no further testing
- Imaging to rule out pancreatic cancer
  - Local expertise
- Structure Function
- Comprehensive characterization
  - TIGAR-O; exocrine or endocrine dysfunction or both
CP Treatment / Pain

• Primary clinical complaint
• Leads to one of the worst QOL scores
• Multiple pain patterns, severity
• Morphology on imaging does not correlate with pain; complex

Pain / PancreasFest Multidisciplinary Study Group

• Etiology of pain
  – Duct obstruction, strictures, pancreatic fibrosis
  – Alterations in nociception
  – Inflammation (mast cells, cytokines, immune cells in nerves)
  – Changes in central processing of pain
  – Maldigestion

http://dx.doi.org/10.1016/j.pan.2015.10.2015
Evaluation

- Pain should be evaluated at every visit for character, frequency and intensity.
  - Constant pain pattern
    - More disability
    - Hospitalizations
    - Pain medication use
    - Lower QOL scores
- QOL
  - Psychological comorbidities should be addressed

Treatment:

- Medical management of the pain
  - Stepwise approach NSAID to narcotic medications for constant severe pain (ibuprofen, tramadol, hydrocodone, morphine....)
  - Long term narcotics warrant pain clinic evaluation
  - Neuromodulating agent, Pregabalin can be considered (RCT)*

*Olesen SS et al. Pregabalin reduces pain in patients with chronic pancreatitis in a randomized controlled trial. Gastroenterology 2011;141(2):536-43
Pain /PancreasFest Multidisciplinary Study Group

• PERT
  – Controversial for pain relief
  – Clearly helps PEI and may help maldigestion symptoms and QOL; nutritional benefits.
    • Vit A,D,E,K, osteoporosis: supplement appropriately

• Antioxidants
  – Controversial and mixed data
    • Less effect in EOTH CP; ? combinations unclear
  – Not routinely recommended

• Behavior Modification
  – Strongly recommended that ETOH and smoking cessation be undertaken and supported
    – Decrease disease progression and pancreatic cancer risk
• Endoscopic Treatment
  – Important role in CP pain therapy
    • Duct obstruction in HOP
    • Pseudocysts, fistula/leaks, PD stones
  – Reduces pain in 65-84% PD stents for strictures
    • No RCT, sham controlled studies
  – Varied techniques (single/multiple stents), ESWL
  – EXPERIENCE counts

• Neurolytic therapy
  – EUS guided CPB not routinely recommended as only 50% responders and short lived effect
  – Surgical division of the splanchnic system similar results
CP/Treatment/Surgical

• Goal is pain relief and preserve tissue
• Procedure type is patient specific
• Pain relief: 80% immediate
  40-50% long-term
• Employed, no ETOH, family support
• mortality <5%, complications 10-25%
• Surgeon/Hospital volume a factor

Pain/PancreasFest Multidisciplinary Study Group

• Surgical TAKE HOME
  – Can be first line therapy
    • Heavy stone burden body/tail
    • Inflammatory mass
  – Indicated with resection or drainage for persistent pain Ø response to medical or endoscopic
  – Resection or drainage should not be done in setting of candidate for TPAIT if available
Pain /PancreasFest Multidisciplinary Study Group

- TPAIT
  - Potential management option for intractable pain in CP, and to impact risk of pancreatic cancer in high risk patients
  - Multidisciplinary team

Bibliography