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Grant System Opens: September 8, 2020
Deadline: December 4, 2020

Read the Grant Flyer, FAQs, or visit the webpage for the RFAs.

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Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

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LIVE VIRTUAL GRAND ROUNDS WEBINAR
ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2020 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2021 for this activity.
MOC QUESTION
If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement. THESE ANSWERS WILL BE REVIEWED.

ACG Virtual Grand Rounds
Join us for upcoming Virtual Grand Rounds!

Week 30: Pouch or True “Ouch”?- Avoid Common Mistakes in the Diagnosis and Management of Ileal Pouch Disorders
Bo Shen, MD, FACG
October 8, 2020 at Noon EDT

Week 31: Special Considerations When Discussing Diet Elimination for EoE
Nirmala Gonsalves, MD
October 22, 2020 at Noon EDT

Visit gi.org/ACGVGR to Register
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Disclosures:

Darwin L. Conwell, MD, MS, FACG
No conflicts of interest.

Jodie A. Barkin, MD
Scientific Advisor for AbbVie and Nestle Health Sciences
Treating the Pain of Chronic Pancreatitis:  
Never Lose Infinite Hope

Darwin L. Conwell, MD, MSc, FACG  
Professor of Medicine  
Floyd Beman Chair in Gastroenterology  
Director, Division of Gastroenterology, Hepatology and Nutrition  
Co-Director, Digestive Disease Area of Concentration  
The Ohio State University Wexner Medical Center  
Columbus, Ohio

MEDICAL PROGRESS

CHRONIC PANCREATITIS

Michael L. Steer, M.D., Irving Waxman, M.D.,  
and Steven Freedman, M.D.

In 1788 Gawley reported on a “free living young man” who had died of emaciation and diabetes and whose postmortem examination revealed multiple pancreatic calculi. In the two centuries since that early description of chronic pancreatitis, literally thousands of reports dealing with this disease have been published, yet chronic pancreatitis remains an enigmatic process of uncertain pathogenesis, unpredictable clinical course, and unclear treatment.

NEJM 1995
SAPE Hypothesis

• Acinar cell stimulation
  — Alcohol, gallstone, TG, oxidative stress

• Sentinel Event
  — Early: pro-inflammatory response
  — Late: Stellate cells, pro-fibrotic response

• Removal of stimulus
  — Abstinence
  — cholecystectomy
  — lipid lowering agents

• Recurrent stimulation
  — Stellate cell mediated peri-acinar fibrosis

Stellate Cells Mediate Fibrosis in CP

Jaster, R., Molecular Cancer 2004.
Risk of RAP is primarily influenced by etiology

Am J Gastro 2012;107:1096-103

Am J Gastro 2009;104:2797-805

Natural history of RAP - CP results in progressive fibrosis and loss of function

Progression from AP to CP: Population studies

<table>
<thead>
<tr>
<th>Country</th>
<th>Years</th>
<th>Sample size</th>
<th>Follow up (years)</th>
<th>Etiology</th>
<th>CP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands</td>
<td>1985-90</td>
<td>9579</td>
<td>5</td>
<td>All</td>
<td>6</td>
</tr>
<tr>
<td>Germany</td>
<td>1997-2004</td>
<td>532</td>
<td>7.8 (median)</td>
<td>All</td>
<td>4</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Alcohol</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Idiopathic</td>
<td>None</td>
</tr>
<tr>
<td>Japan</td>
<td>1987</td>
<td>714*</td>
<td>13 (min.)</td>
<td>All</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Alcohol</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Idiopathic</td>
<td>13</td>
</tr>
<tr>
<td>Denmark</td>
<td>1977-82</td>
<td>352</td>
<td>Until 2008</td>
<td>All</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Alcohol</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-alcohol</td>
<td>20</td>
</tr>
<tr>
<td>USA</td>
<td>1996-2005</td>
<td>6010</td>
<td>~4</td>
<td>All</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>Alcohol</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-alcohol</td>
<td>4</td>
</tr>
</tbody>
</table>


Recurrent Acute Pancreatitis

- ≥2 episodes of AP with resolution of symptomatic and imaging abnormalities between episodes
- Occurs in ~20% of AP patients
- **RAP is the strongest risk factor for progression to CP**
  - HR of 4.57 (95% CI 3.40-6.14)

Mechanistic Definition

- Biomarker Discover / Development
- Yellow Zone – RAP, “Early CP”

Whitcomb, DC, et al., Pancreatology 2016

Conceptual framework – CP

Chronic Pancreatic Pain

- The most common feature of disease
- Detrimental effects on quality of life
- Intermittent, constant
- Response to therapy unpredictable, inconsistent and often inadequate
- Placebo response 20 - 30 %
- Addiction potential 20%

Forsmark C., Gastroenterology 2013
Forsmark C., Liddle, R., Gastroenterology 2012

What Medical Therapy Works?

Answer:

?
Hypothetical Time-Course of Pain in Chronic Pancreatitis

![Graph showing pain intensity over time with different lines indicating natural history without intervention and additional placebo effect]

Figure 2. A hypothetical illustration of the pain intensity over time (solid curve) in a patient with chronic pancreatitis. At the initial course of disease, the pain is fluctuating and may reach a high intensity as illustrated on the y-axis. When pain intensity is the highest, the patient may be desperate and seek invasive treatment (arrow). However, the natural course of disease (in this case, the pain temporarily improves) is not taken into consideration when the outcome of uncontrolled studies of invasive treatment is evaluated. Such a selection bias necessitates a control group subjected to sham surgery/endoscopy before any definitive conclusions regarding effectiveness of treatment can be taken. The placebo effect (stippled green line) can further add to the pain relief after invasive treatments.

Drewes AM, et al, Gut 2018

21

25 y female “Small-duct” CP: I need an Electrician?

- Recurrent abdominal pain
- Fluctuating pancreas enzymes
- Chronic Abdominal Pain

American College of Gastroenterology
19 year old “Big-duct” CP: *I need a Plumber?*

- Recurrent abdominal pain
- Fluctuating pancreas enzymes
- Chronic Abdominal Pain

---

**CP Pain is complex and incompletely understood**

- **Unraveling the mystery of pain in chronic pancreatitis**
  - Burden of disease
  - Pathogenesis Unclear
  - Treatment .....empirical.......invasive methods...... variable outcomes
  - Peripheral sensitization
  - Central sensitization
  - Increased pancreatic nociception

---

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

The majority of CP Patients seen at Tertiary Centers exhibit Extra-pancreatic sources of Pain

Results of Differential Neuroaxial Blockade in Chronic Pancreatitis (n = 23)

<table>
<thead>
<tr>
<th>Pain Type</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral</td>
<td>5 (22%)</td>
</tr>
<tr>
<td>Nonvisceral</td>
<td>18 (78%)</td>
</tr>
<tr>
<td>Central</td>
<td>11</td>
</tr>
<tr>
<td>Somatosensory</td>
<td>4</td>
</tr>
<tr>
<td>Mixed</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>23</strong></td>
</tr>
</tbody>
</table>

Descending Inhibitory Pain Modulation is Impaired in patients with Chronic Pancreatitis

- 25 CP; 15 HS
- Descending pain modulation assessment
  - Noxious inhibitory control
  - Multimodal central processing
  - Evoked brain potentials after rectosigmoid stimulation

- **Conclusion:** CP impairments in pain modulation and central sensitization

- **Treatment of pain should include pancreas and descending pain modulation from supraspinal structures and central nervous system sensitization**

Olesen SS, et al., Clin Gastro Hep 2010

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
Brain metabolites were altered in patients with chronic pancreatitis. High level of glutamate in the anterior cingulate cortex was linked to increased perceived pain, which may indicate a hyperexcitability state of the anterior cingulate cortex in painful chronic pancreatitis.

CP patients had altered functional connectivity within and between brain networks. Altered DMN functional connectivity had an association to cerebral metabolic changes. **Significance:** Altered functional connectivity in CP share similarities with other chronic pain conditions, and neurological disorders such as Alzheimer and depression.
A clinically feasible method for the assessment and characterization of pain in patients with chronic pancreatitis

**Conclusion:** We show normative reference values for a clinically feasible method for assessment and characterization of pain mechanisms in patients with CP. Application of this method streamlines the evaluation of pancreatic pain and may be used to inform treatment. ClinicalTrials.gov id: NCT03434392.

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**Quantitative Sensory Testing**

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Psychiatric Comorbidity in Patients With Chronic Pancreatitis Associates With Pain and Reduced Quality of Life

One hundred seventy-one patients with CP (mean age 53.8 ± 13.7 years, 60% men) were included. Anxiety and depression were present in 80 (46.8%) and 66 (38.8%) patients, with overlap in 50 (29%). Patients with anxiety or depression reported higher pain prevalence, pain severity, and pain interference scores (all \(P < 0.001\)). Psychiatric comorbidities also associated with reduced global health scores and functional subscales (all \(P < 0.001\)) and higher symptom burden (\(P < 0.03\)). An independent association was noted between global health status and depression (\(P < 0.001\)).

**RESULTS:**

Psychiatric comorbidities are prevalent in patients with CP and associated with pain and QOL. Where the effect of anxiety or QOL may be mediated via pain, depression is independently related to QOL. These findings warrant consideration in the management of patients with CP.
Constant-severe pain in chronic pancreatitis is associated with genetic loci for major depression in the NAPS2 cohort


Received: 7 May 2020 / Accepted: 17 June 2020 / Published online: 17 July 2020
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• GWAS STUDY

• Fifteen loci associated with constant severe pain (p<0.00001) were found to be in or near depression-associated genes including ROBO2, CTNND2, SGCZ, CNTN5 and BAIAP2.

• Approximately 18% of patients with chronic pancreatitis also experience depression

• Pain can increase the severity of depression, and vice versa

• Our findings suggest that there is an overlap of depression-associated genes and constant-severe pancreatic pain.

J Gastro 2020

Mechanism Based Approach to Chronic Pancreatitis Pain

"Wiring problem": peripheral sensitization
1. neuropathy
2. CNS changes

"Plumbing problem": duct stenosis and stones
1. Local: inflammatory mass, pseudocysts etc.

Extra-pancreatic complications ~ e.g. peptic ulcer
1. Extrapancreatic complications ~ e.g. peptic ulcer

Inflammation ~ e.g. cytokines
1. Tissue hypertrophy

Drug induced bowel dysfunction
1. Surgical/endo-scopical complications

Others
1. increased sympathetic activity
2. enteric nervous system changes
3. mesenteric ischaemia
4. other concomitant diseases
5. opioid induced hypoperfusion

Lack of hormones
1. Matility disorders & bacterial overgrowth

Increased CCK production
PERT may decrease CP pain by decreasing CCK mediated stimulation or improving digestion

- Uncoated preparations*
  - CCK-RF mechanism
  - Trypsin mediated

- Coated preparations
  - maldigestion
  - Lipase mediated

- Metanalysis confounded by including both types of preparations**

*Slaff J, Gastroenterology 1984
**Brown, A, Am J Gastroenterol 1997

Antioxidants have also been shown in RCTs to reduce CP pain in selected patient populations*

- Several randomized trials
  - Variable results
  - Different antioxidant preparations
  - Heterogeneous populations
    - Opiate addiction
    - Alcohol use
    - Variability in use of PERT
    - Prior pancreatic surgery
    - Different disease severities
  - Varying duration of treatment

- Safe, non-toxic
  - Worth considering

*Bhardwaj P et al, Gastroenterology 2009
Siriwandena AK, Gastroenterology 2012
Braganza JM, Gastroenterology 2013
Talukdar R et al., Gastroenterology 2013
*Dhingra R et al., Pancreas 2013
Pregabalin reduces pain and improves QOL in chronic pancreatitis in a RCT

METHODS:
- RCT, 64 patients
- Pregabalin or placebo (control) for 3 consecutive weeks.

RESULTS:
- Pregabalin, compared with placebo
  - Pain relief after 3 weeks of treatment (36% vs 24%; P = .02).
  - Improved health status was higher in the pregabalin than the control group (44% vs 21%; P = .048).

CONCLUSIONS:
- In a placebo-controlled trial, pregabalin is an effective adjuvant therapy for pain in patients with CP.

Olesen SS et al, Gastroenterology 2011

Tramadol provides effective analgesia in a RCT with less gastrointestinal side effects than morphine for the treatment of CP Pain

- Tramadol vs. morphine
  - severe chronic pancreatitis pain
  - interaction with gut motor function.
- Oral dose titration
  - double-blinded, RCT
  - 25 CP patients
- Outcomes: Pain intensity, Patient rated analgesia

Results
- Tramadol had statistically favorable:
  - Orocecal transit (P < 0.05), colonic transit times (P < 0.05), Rectal distension threshold pressures (P < 0.01).
- Tramadol interfered significantly less with gastrointestinal function and was more often rated as an excellent analgesic than morphine.

Wilder-Smith CH et al. Dig Dis Sci 1999
Long-term enteral nutrition improves body weight and decreases abdominal pain in CP

- Retrospective, n=57
- Small-bowel access was obtained by PEG/J in 53 patients and by DPEJ
- Duration of enteral feeding was 3-6 months
- Average body weight significantly increased from 64.8 kg at day 1 to 69.1 kg at day 180 (p < 0.001).
- Abdominal pain decreased from 96% to 48% at 90 days (p<0.001) and 23% at 180 days (p < 0.001)
- Narcotic use decreased from (p<0.001)
- Gastrointestinal symptoms decreased from 90 % to 14.6 % (p <0.001)


Pain Studies in Chronic Pancreatitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Interventions</th>
<th>Follow-up</th>
<th>Pain relief (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosch et al.22</td>
<td>Cohort</td>
<td>1018</td>
<td>Endoscopy (including ESWL)</td>
<td>4.9 years</td>
<td>65</td>
</tr>
<tr>
<td>Tsukumo et al.23</td>
<td>Cohort</td>
<td>57</td>
<td>Endoscopy (including ESWL)</td>
<td>1 year</td>
<td>63</td>
</tr>
<tr>
<td>Duronnoix et al.24</td>
<td>RCT</td>
<td>55</td>
<td>ESWL with without subsequent endoscopy</td>
<td>2 years</td>
<td>55 vs 62 (p=0.051)</td>
</tr>
<tr>
<td>Conventional surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dite et al.25</td>
<td>RCT</td>
<td>72</td>
<td>Endoscopy (without ESWL) versus surgery</td>
<td>5 years</td>
<td>61 vs 86 (p=0.002)</td>
</tr>
<tr>
<td>Cahen et al.26</td>
<td>RCT</td>
<td>38</td>
<td>Endoscopy (including ESWL) versus surgery</td>
<td>2 years</td>
<td>32 vs 75 (p=0.007)</td>
</tr>
<tr>
<td>Cahen et al.27</td>
<td>Long-term results RCT</td>
<td>31</td>
<td>Endoscopy (including ESWL) versus surgery</td>
<td>&gt;4 years</td>
<td>38 vs 80 (p=0.042)</td>
</tr>
<tr>
<td>TPAT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bellin et al.28</td>
<td>Cohort</td>
<td>215</td>
<td>TPAT</td>
<td>10 years</td>
<td>82</td>
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<tr>
<td>Neuropathic pain medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olsen et al.29</td>
<td>RCT</td>
<td>64</td>
<td>Pregabalin versus placebo</td>
<td>3 weeks</td>
<td>36 vs 24 (p=0.02)</td>
</tr>
</tbody>
</table>

*Complete and partial pain relief combined.

References:

The Spanish Pancreatic Club's recommendations for the diagnosis and treatment of chronic pancreatitis: Part 2 (treatment)

- NSAIDS
- Pregabalin
- Antioxidants
- PERT
- Tramadol
- Early Invasive Therapy
- Opioids
- Late Invasive Therapy

de-Madaria E, et al., Pancreatology 2013

ACG Clinical Guideline: Chronic Pancreatitis

Chronic pancreatitis (CP) is historically defined as an irreversible inflammatory condition of the pancreas leading to varying degrees of exocrine and endocrine dysfunction. Recently however, the paradigm for the diagnosis has changed in that it breaks with the traditional clinicopathologic-based definition of disease, focusing instead on diagnosing the underlying pathologic process early in the disease course and managing the syndrome more holistically to change the natural course of disease and minimize adverse disease effects. Currently, the most accepted mechanistically derived definition of CP is a pathologic fibroinflammatory syndrome of the pancreas in individuals with genetic, environmental, and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress. The most common symptom of CP is abdominal pain, with other symptoms such as exocrine pancreatic insufficiency and diabetes developing at highly variable rates. CP is most commonly caused by toxins such as alcohol and tobacco use, genetic polymorphisms, and recurrent attacks of acute pancreatitis, although no history of acute pancreatitis is seen in many patients. Diagnosis is made usually by cross-sectional imaging, with modalities such as endoscopic ultrasonography and pancreatic function tests playing a secondary role. Total pancreatectomy represents the only known cure for CP, although difficulty in patient selection and the complications inherent to this intervention make it usually an unfeasible option. This guideline will provide an evidence-based practical approach to the diagnosis and management of CP for the general gastroenterologist.

What do we tell our patients

- **Lifestyle modification**
  Alcohol abstinence, smoking cessation

- **Non-narcotic Management**
  - Gabapentin, Pregabalin
  - Antioxidants
  - *Tramadol*
  - Uncoated PERT
  - Pancreatic rest: NJ feeding or TPN

- **Endoscopic Therapy + ESWL**: short term, older patients, comorbidities

- **Surgery**: long term

- **Narcotic analgesics**: Opiates, Pain Therapy Consultation, psychology, anesthesia, detox / wean narcotic dose

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*ACG Clinical Guideline: Chronic Pancreatitis*

Timothy B. Gardner, MD, MS, FACG,
Douglas G. Adler, MD, FACG,
Chris E. Fornmark, MD, FACG,
Brian G. Sauer, MD, FASG (Chairman), FACG (Methodologist),
Jason R. Taylor, MD, and David C. Whelan, MD, PhD, FACG

<table>
<thead>
<tr>
<th>Table 2: Recommendations on the management of CP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis of CP</strong></td>
</tr>
<tr>
<td>1. We recommend CT performed for the first time diagnosis of CP. Other tests should be the first test for the diagnosis of CP.</td>
</tr>
<tr>
<td>2. We suggest performing MRI/CT when the diagnosis of CP is not confirmed with the clinical symptoms and non-invasive (high conditional recommendation, low quality of evidence).</td>
</tr>
<tr>
<td>自然</td>
</tr>
<tr>
<td>7. We recommend surgical resection or endoscopic therapy in patients with obstructive CP, severe pain</td>
</tr>
<tr>
<td>8. We suggest using non-invasive (high conditional recommendation, moderate quality of evidence).</td>
</tr>
<tr>
<td>9. We do not recommend the use of endoscopic therapy in CP with pain, although the benefit of pain reduction is likely conditional recommendation, moderate quality of evidence.</td>
</tr>
<tr>
<td>10. We suggest considering other options for treatment of pain in CP, conditional recommendation, very low quality of evidence.</td>
</tr>
<tr>
<td>11. We suggest PERT in patients with CP if there is no pancreatic insufficiency to improve the outcomes of radiation treatment.</td>
</tr>
<tr>
<td>12. We suggest considering other options for treatment of pain in CP, conditional recommendation, very high quality of evidence.</td>
</tr>
<tr>
<td>13. We suggest PERT in patients with CP if there is no pancreatic insufficiency to improve the outcomes of radiation treatment.</td>
</tr>
<tr>
<td>14. We suggest considering other options for treatment of pain in CP, conditional recommendation, very high quality of evidence.</td>
</tr>
</tbody>
</table>

---

A. Cahen DL, NEJM 2007; Dite P, Endosc 2003
CP Pain Management

- DEFINITIVE DIAGNOSIS
- MECHANISTIC DEFINITION
- Smoking, alcohol cessation
- Psychological Assessment
- Assess for Opioid Dependency
- Mechanistic Pain Characterization
  - Quantitative sensory testing
  - Nerve blockade (CPB or DNB)
- Antioxidants (50:50)
- Tramadol (BEFORE NARCOTICS)
- Pregabalin
- WHO ANALGESIC LADDER
- Pancreatic Rest – N2, TPN

- DUCT MORPHOLOGY
  - Surgical Therapy – Beger Procedure
  - Large duct
  - Endoscopic Therapy
    - Large duct, strictures, stones
  - Total Pancreatectomy with islet cell transplantation
    - Small duct, selected patients, psychiatry, chemical dependency, opioid dependence, support system

- RANDOMIZED TRIALS – Endpoints needed
  - Molecular targeted therapy – TRPV1, NGFs, Mast cells, cytokines
  - Cognitive Behavioral Therapy
  - Drug Repurposing: NSAIDS, HMG CoA, CFTR modulators
  - Celiac Block: newer agents

25 year old “Small duct” CP: I need an electrician?

- Celiac plexus block
- Deep Brain Stimulation Study
- Nasojejunal feeding x 3-4 mo
- Total Parenteral Nutrition x 3-4 mo
- Pain 6-8/10
- Chronic Narcotics
- SSRIs, TCAs

• 1st Pancreas Center: EUS – 4 criteria / 1 hour Dreiling PFT = 50 meq/L
  ………………… 2 years later….
• 2nd Pancreas Center: EUS – 6 criteria / 1 hour cPFT = 48 meq/L

• Considering Total Pancreatectomy with Islet Cell Transplantation
19 year old “Big duct” CP: I need a Plumber?

- Chronic Pain; Borderline Diabetes mellitus
- Exocrine Insufficiency: steatorrhea
- Fentanyl lollipops 800-1600 mcg every 6h
- Methadone 10-20 mg every 8 h
- Peustow procedure

- Frey Procedure - ineffective
- Total Pancreatectomy with Islet Cell Transplant
- Pain continues; “brittle” diabetes

“We must accept finite disappointment, but never lose infinite hope.”
Rev. Dr. Martin Luther King, Jr.
There is HOPE !!

Research Gaps and Opportunities

• Improve and accurate assessment of maldigestion and EPI.
• Establish simpler, less invasive tools to measure acinar and ductal cell function from more easily obtained biological specimens such as urine or blood to screen for pancreatic disease.
• Develop RAP and DP biomarkers that can be used to better define the stage, determine prognosis, assess severity, and stratify patients for medical or surgical intervention using the mechanistic definition framework.
• Provide evidence-based recommendations for proper dietary intake and the requirements for PERT (initiation, dose, timing, follow-up).
• Develop enzyme products requiring fewer pills and with better compliance and potency.

Chronic Pancreatitits: Managing a Difficult Disease

There are no current therapies to delay or retard disease progression, but there are ongoing efforts to more fully understand the natural history of chronic pancreatitis and underlying mechanisms of disease. These studies are expected to provide insights that will transform our approach to disease management and provide increased hope to patients.


Conference Report

Chronic Pancreatitis in the 21st Century - Research Challenges and Opportunities

Summary of a National Institute of Diabetes and Digestive and Kidney Diseases Workshop

There are no current therapies to delay or retard disease progression, but there are ongoing efforts to more fully understand the natural history of chronic pancreatitis and underlying mechanisms of disease. These studies are expected to provide insights that will transform our approach to disease management and provide increased hope to patients.

Research Gaps and Opportunities

• Develop long-term primary acinar and ductal epithelial cell culture models.
• Explore co-culture models (eg, acinar-duct, duct-islet, acinar-islet) to identify factors that regulate exocrine cell function and restitution.
• Define mechanisms by which gene mutations/variants cause pancreatic inflammation, ductal cell malfunction, and acinar cell loss.
• Design novel therapies that target restoring pancreatic acinar cells and/or manipulate ductal cells (ie, gene and cell-based therapies, CRISPR/Cas9, CFTR correctors and potentiators).
• Develop experiments to define the critical age and time for intervention to reestablish appropriate stem cell niches for cell-based therapies in diseases that damage the exocrine pancreas.

Uc A., Pancreas 2016.
Consortium for the Study of Chronic Pancreatitis
Diabetes and Pancreatic Cancer

I. Established the Largest Prospective cohort of CP: PROCEED

PROspective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies
Rationale and Study Design for PROCEED From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer

PROCEED Study Objectives

• **Primary**
  1. To establish a model of *longitudinal research cohort of adults with CP* and its complications
  2. To estimate the **risk of progression to suspected CP to definite CP**, development of new-onset diabetes and exocrine insufficiency in definite CP, and study how the risks are influenced by patient characteristics and conditions
  3. To test **predictive capability of candidate biomarkers** for diagnosis and prognosis of CP
  4. To develop a framework for conducting biomarker, genetic and mechanistic studies using clinical information and the biorepository developed as part of the longitudinal research cohort

• **Secondary (several)**

II. Established SOPs for collection of Biospecimens in CP cohort

**CPDPC Conference Report**

*Standard Operating Procedures for Biospecimen Collection, Processing, and Storage*

*From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer*

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Zachary M. Miller, MD, PhD,** David M. Thomas, MD,** Allie U., MS,** MM, E., MD,** Mark E. Lovet, MD, PhD,**

and Darwin L. Conner, MD, on behalf of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC)

III. Established SOPs for recording CT and MRI findings of CP

Reporting Standards for Chronic Pancreatitis by Using CT, MRI, and MR Cholangiopancreatography: The Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer


Current Recruitment Status - PROCEED
IV. Established the PROCEED Biorepository which is ready for use (>100,000 aliquots already)

- According to the PRoBE design

<table>
<thead>
<tr>
<th>Center</th>
<th>Samples Shipped (N of Shipments)</th>
<th>Samples Collected</th>
<th>% Shipped</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston</td>
<td>3,200 (11)</td>
<td>6,005</td>
<td>99</td>
</tr>
<tr>
<td>Delaware</td>
<td>5,282 (9)</td>
<td>6,169</td>
<td>94</td>
</tr>
<tr>
<td>Indiana</td>
<td>3,320 (3)</td>
<td>17,701</td>
<td>53</td>
</tr>
<tr>
<td>West Coast</td>
<td>2,051 (3)</td>
<td>15,070</td>
<td>14</td>
</tr>
<tr>
<td>Stanford</td>
<td>1,202 (10)</td>
<td>11,562</td>
<td>95</td>
</tr>
<tr>
<td>CRU</td>
<td>5,390 (9)</td>
<td>12,381</td>
<td>96</td>
</tr>
<tr>
<td>UPMC</td>
<td>16,420 (14)</td>
<td>15,157</td>
<td>99</td>
</tr>
<tr>
<td>Points</td>
<td>4,877 (3)</td>
<td>6,020</td>
<td>79</td>
</tr>
<tr>
<td>Vawter</td>
<td>2,404 (9)</td>
<td>6,500</td>
<td>33</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>63,871 (99)</td>
<td>100,011</td>
<td>99</td>
</tr>
</tbody>
</table>

*More samples are excluded from this table, so those containers to be shipped from the recipe College of Medicine Microbiome Center. Bure rate collection and shipping is presented in Table 2 below.

- Legacy samples outside of PROCEED also available for exploratory work

Review of summary data - PROCEED
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

Methods: Single-blinded randomized placebo-controlled multicenter trial aims to enroll 280 youth (ages 10–18) with ARP/CP and their parents from twenty-one INSPIRE (International Study Group of Pediatric Pancreatitis: In search for a cure) centers.

Web-based cognitive-behavioral intervention for pain in pediatric acute recurrent and chronic pancreatitis: Protocol of a multicenter randomized controlled trial from the study of chronic pancreatitis, diabetes and pancreatic cancer (CIPDCP)

American College of Gastroenterology
IMPACT Study – Pilot RCT

• **Aim 1**
  – To refine an existing internet-delivered pain self-management program for use in **ADULT CP patients**

• **Aim 2**
  – To conduct a pilot randomized controlled trial of the refined CBT program versus wait-list control in adult CP patients to evaluate feasibility and acceptability

• **Aim 3**
  – To generate pilot data regarding effects of internet-delivered CBT on symptoms and quality of life in adult CP patients

**IMPACT Study**

**Study sites and community recruitment**

**Clinic recruitment from the CPDPC sites:**
- Indiana University
- Mayo Clinic Rochester
- Stanford University
- Ohio State University
- UPMC
- University of Minnesota

**Social media recruitment through the National Pancreas Foundation (NPF):**
- Facebook, Instagram, Twitter,
- [NPF website and newsletters](#)
IMPACT Study
Current Status and Future Plans

T1: Baseline assessment
T2: 2 months following baseline
T3: 3 months following T2

Measures/Outcomes
• Brief Pain Inventory
• PROMIS-29 Profile
• PANQOL
• SF-12 Short Form Health Survey
• Pain Disability Index
• PROMIS Alcohol Use Short Form
• Chronic Pain Self-Efficacy Scale
• Medication/Opioid Use
• Online 7-day pain diary
• Qualitative interview

• Target = 30 participants
• Randomized
  • Wait list control vs. CBT
• Recruitment completed
• 80% female
• Age range: 23-72 years

Plans
– Results expected Summer 2020
– Grant application anticipated based on results

Endoscopic Therapy on Quality of Life and Pain in Chronic Pancreatitis (The EQuiPP Study)
Samuel Han, MD
The Ohio State University

Aim 1: To assess the impact of pancreatic endotherapy on disease-specific quality of life and overall quality of life
• Measure quality of life before and after endotherapy

Aim 2: To evaluate the impact of pancreatic endotherapy on pain and predict response to PET based on specific pain patterns
• Measure pain levels before and after endotherapy
• Use quantitative sensory testing to determine pain profile and identify whether response to endotherapy can be predicted based on pain profile

Goal: Develop personalized, endoscopic approach to treatment in patients with chronic pancreatitis
FLOWCHART

Initial Enrollment with baseline demographics, current pain medication use, PANcreatitis Quality of Life Instrument (PANQOLI), PROMIS-29, PROMIS Nociceptive Pain Quality, PROMIS Neuropathic Pain Quality, Pain-related Self-Efficacy Scale, Concerns about Pain Short Form, Quantitative Sensory Testing (QST) and Biorepository collection

↓

Completion of pancreatic endotherapy

↓

Administer same questionnaires at 1, 3, 6, and 12 months follow-up and 2nd Biorepository collection at 6 months

Mechanism-based Approach to Pain in Chronic Pancreatitis (MAP-CP)

PI: Jami Saloman, PhD
Co-I: Liang Li, PhD and Dhiraj Yadav, MD, MPH

Hypothesis: Patient-derived information (patient reports and biospecimens) can be used to identify mechanistic pain phenotype and inform management of CP-related pain.
Rationale

- Pain affects ~80% of CP patients
- 2/3 of CP patients fail to achieve adequate relief
- Involves nociceptive and/or neuropathic mechanisms
- Efficacy of Interventions depend on pain mechanism
- Neuropathic and nociceptive pain can involve distinct inflammatory mediators and neuromodulators
- Serum analysis of neuromodulators can distinguish nociceptive and neuropathic pain

MAP-CP

Aim 1: Cross-sectional Analysis of CP pain
1. Characterize pain phenotypes as determined by nociceptive and neuropathic PROMIS Q
2. Cross-sectional analysis to identify biochemical signature for each pain phenotype
3. Correlate with other pain or disease related factors (e.g. pain intensity, pain frequency, quality of life measures)

Aim 2: Longitudinal analysis of natural course of CP pain
1. Determine if pain phenotype changes between visit #1 and #2
2. Test biomarkers by determining if any changes in pain type (nociceptive, neuropathic, mixed) correlate with changes in serum or other pain related factors.

Fig 1. Preliminary analysis. The distribution of patients with definite CP by pain mechanism as determined via PROMIS® pain mechanism surveys. (n=267)
Characterization of the CP Pain Syndrome may be Critical in Targeting Effective Neuropathic Therapy

- **Intrapancreatic**
  - Neuropathic mechanisms
  - TRPV1, NGF inhibitors
  - Secretin washout (trypsin)
  - Antioxidants (inflammation)

- **Extrapancreatic**
  - DRG and spinal cord hypersensitivity
  - Enkephalin gene therapy
  - RFA, SC stimulation

- **Cerebral cortex adaptation**
  - Pregabalin

Demir et al., Langenbecks Arch Surg 2011

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Window of Opportunity = “Minimal Change” – Early Stage .....CP

Phase 1/2 Trial of Indomethacin in Chronic Pancreatitis
(The PAIR Trial - 1R21DK117212-01A1)

MCCP = Minimal Change Chronic Pancreatitis


Mayo Clinic and Ohio State

• Anti-inflammatory drugs such as indomethacin, which decrease prostaglandin E2 (PGE₂) production, could be repurposed to lessen the severity of CP.
• Prospective, RCT study, indomethacin or placebo will be given to patients with CP
• Pancreas juice and saliva PGE₂ levels will be measured, in order to determine whether standard doses of indomethacin effectively suppress pancreatic PGE₂ production
• Potential large scale, multicenter trials, with the goal of improving pain and quality of life in patients with this chronic illness.

Mayo Clinic and Ohio State
Phase 1/2 Trial of Indomethacin in Chronic Pancreatitis
(The PAIR Trial-1R21DK117212-01A1)

Mechanism Based Approach to Chronic Pancreatitis Pain: Quality of Life

American College of Gastroenterology
The Pain of Chronic Pancreatitis:

*There is Always Hope*

Hope in the face of difficulty. Hope in the face of uncertainty. The audacity of Hope. In the end, that is God’s greatest gift to us. A belief in things not seen. A belief that there are better days ahead.

Barack Obama

*NIH Consortium for the Study of Chronic Pancreatitis*

*Diabetes and Pancreatic Cancer*
The Pain of Chronic Pancreatitis: 
There is Always Hope

NIH Consortium for the Study of Chronic Pancreatitis
Diabetes and Pancreatic Cancer

Questions?
Darwin L. Conwell, MD, MS, FACG
Jodie A. Barkin, MD