Participating in the Webinar

All attendees will be muted and will remain in Listen Only Mode.

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.
How to Receive CME and MOC Points

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, 2021 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, 2022 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 16, 2021
Opioid Induced Esophageal Dysfunction: What to Know and How to Manage It
Marcelo F. Vela, MD, MSCR, FACG
April 22, 2021 at Noon Eastern

Week 17, 2021
Chromoendoscopy in IBD Surveillance: Always, Sometimes or Never?
Samir A. Shah, MD, FACG
April 29, 2021 at Noon Eastern

Visit gi.org/ACGVGR to Register

Disclosures:

Speaker:
Jodie A. Barkin, MD
Consultant: AbbVie Inc, Nestle Health Sciences, HealthiVibe LLC; Grant Support: Cystic Fibrosis Foundation DIGEST Grant; Grant Support (prior): AbbVie, Cook Endoscopy.

Moderator:
C. Roberto Simons-Linares, MD
Dr. Simons Linares, faculty for this educational event, has no relevant financial relationship(s) with ineligible companies to disclose.

*All of the relevant financial relationships listed for these individuals have been mitigated.
Principles and Pitfalls in Exocrine Pancreatic Insufficiency

Jodie A. Barkin, M.D.

Assistant Professor of Clinical Medicine
Assistant Medical Director, National Pancreas Foundation Center of Excellence at the University of Miami
Associate Director, Adult Cystic Fibrosis Center at the University of Miami

University of Miami, Leonard M. Miller School of Medicine,
Department of Medicine, Division of Gastroenterology,
Miami, Florida, USA

Learning Objectives

• Identify the etiologies of exocrine pancreatic insufficiency.

• Recognize the symptoms of exocrine pancreatic insufficiency.

• Understand the impact and consequences of untreated exocrine pancreatic insufficiency.
Case Presentation

• 46 y/o M, hx of recurrent acute pancreatitis x 4 (last episode 7 years prior) due to alcohol consumption with alcohol cessation 7 years ago

• Complains of chronic dull epigastric pain, worse post-prandially

• Associated bloating

• Notes a 15 pound unintentional weight loss in 6 months

• Bowel habits: 2 soft stools daily that float in the toilet bowl with small oil droplets floating in the water

Case Presentation: Part Two

Physical Exam:
• Vitals: T 36.8C; HR 84 bpm; RR 12; BP 108/74; O2 Sat 99% on room air, BMI 20.8
• Gen: AAOx3, NAD
• HEENT: NC/AT, Oral Mucosa Moist, Anicteric Sclera
• Neck: Supple, Trachea Midline, no JVD
• Cardio: regular rate and rhythm, no M/R/G
• Pulm: Breathing comfortably; CTAB
• Abdomen: Bowel sounds present, soft, nondistended, minimal epigastric tenderness, no rebound, no guarding, no hepatosplenomegaly, no Murphy’s sign
• Ext: 2+ pulses bilaterally, no peripheral edema
• Neuro: AAOx3, non-focal.
• Psych: Normal mood and affect, no SI/HI

Labs:
• CBC: normal
• CMP: normal; normal Cr and LFTs
• Lipase: 48 U/L
• CA 19-9: 5 U/mL (normal <37)
• INR 1.4
• Vitamin D (25-OH): 20 ng/mL (normal >30)
• Vitamin A & E normal
• Hemoglobin A1C: 7.1%
• Fecal Elastase: 74 μg/g (Normal: >200 μg elastase/g fecal material; moderate pancreatic insufficiency 100-200μg/g; severe pancreatic insufficiency <100 μg/g)
A diagnosis of chronic pancreatitis with exocrine pancreatic insufficiency is made

Exocrine Pancreatic Insufficiency: Outline

- Definition
- Etiologies/Pathophysiology
- Epidemiology
- Symptoms
- Diagnosis
- Management
- Consequences of Exocrine Pancreatic Insufficiency
- Barriers to Care
Overall Progression of Pancreatic Disease

3rd Most Common Reason for GI Related Hospitalization in U.S.¹

- **Acute Pancreatitis**
  - Single Episode
  - Recurrent OR Complication

- **Recurrent Acute Pancreatitis**
- **Chronic Pancreatitis**
- **Pancreatic Cancer**

~ 280,000/year total; ~ 150,000/year incident in U.S.¹,²

~ 40-50,000 of the 150,000²

---

Acute Pancreatitis Hospitalizations Are Increasing

AP Cases: 9.48/1000 → 12.19/1000; p < 0.001

<table>
<thead>
<tr>
<th>Year</th>
<th>2002</th>
<th>2013</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP Incidence</td>
<td>9.48/1000</td>
<td>12.19/1000</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>In-Hospital Mortality</td>
<td>2.99/1000</td>
<td>2.04/1000</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Mean Length of Stay</td>
<td>6.99 days</td>
<td>5.74 days</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Mean Hospital Cost</td>
<td>$27,827</td>
<td>$49,772</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

Acute Pancreatitis is the First Pancreatic Event in Half of Patients with Chronic Pancreatitis

1. Can We Prevent the First AP Episode?
2. Can We Break the Cycle?

Conclusions:
- Half of CP patients first presented with AP
- Half had recurrent AP
- In nearly 40% of CP cases, this sentinel AP episode may be the mechanism for CP

4. Can We Prevent the First AP Episode?
5. Can We Break the Cycle?

Exocrine Pancreatic Insufficiency: Definition

- Exocrine Pancreatic Insufficiency a.k.a. EPI
- Relative lack of functional pancreatic enzymes at the appropriate time during the digestive process resulting in maldigestion
  - Insufficient pancreatic enzyme secretion (acinar function)
  - Insufficient bicarbonate secretion (ductal function)
Causes of Exocrine Pancreatic Insufficiency

Lindkvist B. World J Gastroenterol 2013;19(42):7258-66

EPI Etiologies

<table>
<thead>
<tr>
<th>Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pancreatitis</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>Pancreatic duct obstruction</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Shwachman-Diamond syndrome</td>
</tr>
<tr>
<td>Pancreatic resection</td>
</tr>
<tr>
<td>Small bowel resection/Roux-en-Y</td>
</tr>
<tr>
<td>Celiac disease</td>
</tr>
<tr>
<td>Hemochromatosis or Alpha 1 antitrypsin (rare)</td>
</tr>
<tr>
<td>Zollinger Ellison syndrome (enzyme inactivation) uncommon</td>
</tr>
</tbody>
</table>

American College of Gastroenterology
**Exocrine Pancreas Physiology: Part 1**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Mediator</th>
<th>Secretion %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalic</td>
<td>Vagus</td>
<td>20-25%</td>
</tr>
<tr>
<td>Gastric</td>
<td>Food in stomach &amp; Vagus</td>
<td>10%</td>
</tr>
<tr>
<td>Intestinal</td>
<td>Hormonal (secretin &amp; CCK) &amp; neural</td>
<td>50-80%</td>
</tr>
<tr>
<td>Absorbed nutrient</td>
<td>Amino acids may promote secretion</td>
<td></td>
</tr>
</tbody>
</table>

Chandra R, Liddle RA. Regulation of Pancreatic Secretion. Pancreapedia 2015. Figure: UpToDate, Courtesy of Dr. Tyler Stevens & the Cleveland Clinic Foundation.

**Exocrine Pancreas Physiology: Part 2**

- Normal pancreatic function will produce approximately 700,000 lipase units per meal (varies by meal)
- Fat maldigestion when < 10% of residual lipase function

Figure: UpToDate, Courtesy of Dr. Tyler Stevens & the Cleveland Clinic Foundation.
Development of EPI after Acute Pancreatitis

- **Study Design:** Systematic Review & Study Level Meta-Analysis of 32 Studies of 1495 AP Pts evaluating development of EPI after AP

**Results:**
- **Pooled EPI Prevalence After AP: 27.1%** (95% CI 20.3-35.1%)
- EPI more common in Alcoholic AP than Biliary AP or other AP etiologies using Fecal Elastase testing (22.7% vs. 10.2% vs. 13.4%; p=0.02)
- EPI more common after severe AP than mild AP (33.4% vs. 19.4%; p=0.049)
- EPI somewhat more common if necrosis present (32.0% vs. 18.9%; p=0.053)
- Findings confirmed in a subsequent systematic review and meta-analysis of 39 studies of 1795 pts, EPI prevalence of approximately 35% after AP; and more prevalent in Alcoholic etiology, severe AP and with necrosis present.


Chronic Pancreatitis: Epidemiology

**Etiology – WOMEN²**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>32%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>30%</td>
</tr>
<tr>
<td>Genetic</td>
<td>12.8%</td>
</tr>
<tr>
<td>Obstructive</td>
<td>12%</td>
</tr>
</tbody>
</table>

**Etiology - MEN²**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>58.5%</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>18%</td>
</tr>
<tr>
<td>Genetic</td>
<td>7.3%</td>
</tr>
<tr>
<td>Obstructive</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

Exocrine Pancreatic Insufficiency (EPI) in Chronic Pancreatitis

- Inability to properly digest food due to a relative lack of functional pancreatic enzymes
- Etiology:
  - Destruction of pancreatic parenchyma and loss of acinar cells
  - Obstruction of the pancreatic duct secondary to strictures and stones
- Prevalence and severity of EPI increases with duration of CP
  - 6-22% at time of CP diagnosis
  - 28% by 5 years post-CP diagnosis
  - 50% by 12 years post-CP diagnosis
- More common in alcoholic than non-alcoholic CP (41% vs. 19%)


Exocrine Pancreatic Insufficiency in Pancreatic Cancer

Resectable Pancreatic Cancer:
- 25-45% have pre-operative EPI
- 50-80% of patients continue to experience EPI after pancreatic surgery

Unresectable PC:
- EPI is common (>50%) and progressive over time

EPI in Celiac Disease

- **Prevalence of Celiac Disease in U.S.:** ~1%

- **Pathophysiology:** Celiac Disease $\rightarrow$ small bowel mucosal damage $\rightarrow$ impaired enteric mediated hormonal stimulation to pancreas (CCK) and loss of enterokinase $\rightarrow$ EPI

- **Aim:** Determine prevalence of EPI in Celiac Disease at diagnosis & with gluten free diet treatment

- **Methods:** Systematic review & Meta-analysis

- **Population:** 460 Celiac disease pts; 34% male, mean age 44.1 years
EPI in Newly Diagnosed Celiac Disease

- Prevalence Range: 10.5% - 46.5%
- Pooled: 26.2% (95% CI 8.43% - 43.92%, Q = 2.24, I^2 = -33%)


EPI in Celiac Disease Patients on Gluten-Free Diet

- Prevalence Range: 1.9% to 18.2%
- Pooled: 8% (95% CI 1.52% - 14.8%, Q = 4.42, I^2 = 9.59%)

Symptomatic Celiac Disease Increases EPI Prevalence

Patients with newly diagnosed CD are significantly more likely to have EPI compared to those patients treated with GFD (p = 0.031).

Prevalence of EPI: Symptomatic CD patients on GFD (28.4%) vs. Asymptomatic CD patients on GFD (3%) (P<0.001)

EPI in Symptomatic CD on GFD: 28.4%
EPI in Asymptomatic CD on GFD: 3%


EPI Prevalence Varies by Etiology

- Chronic pancreatitis: 30% in patients with mild disease; 85% with severe disease
- Cystic fibrosis: Approximately 65% of newborns
- Diabetes Type 1: 26-44%
- Type 2: 12-20%
- HIV/AIDS: 1-45%
- Intestinal disorders: 4-6%
- Irritable bowel syndrome: 4%
- Coeliac disease: 12-30%
- Inflammatory bowel disease: 19-30%
- Inoperable pancreatic cancer: 50-100%
- Distal pancreatectomy: 19-80%
- Whipple surgery: 56-98%
- Shwachman-Diamond syndrome: 82%
- Johnson-Blizzard syndrome: High

Clinical Symptoms of Exocrine Pancreatic Insufficiency

- Bloating & Increased Flatulence
- Abdominal Discomfort & Sitophobia
- Diarrhea
- Steatorrhea
- Malnutrition
- Weight Loss
- Vitamin Deficiencies (A, D, E, K)
- Micro-Nutrient Deficiencies


EPI: Diagnosis Using a Constellation of Factors

- Comorbid Conditions
- Nutritional Sequelae
- Clinical History
- Risk Factors
- Symptoms

Diagnosis of Exocrine Pancreatic Insufficiency

- Quantitative 72-hour fecal fat (using a standardized fat intake diet)
- Endoscopic pancreatic function testing via Dreiling tube/endoscopy (+/- use of secretin) – measuring bicarbonate secretion
- Secretin enhanced MRCP pancreatic function testing
  - **Fecal elastase-1 (FE-1) (Traditionally EPI < 200 mcg/g)**
    - FE-1 performance characteristics by meta-analysis1:
      - FE-1 vs. Secretin Stimulation: FE-1 sensitivity 77%, specificity 88%
      - FE-1 vs. Quant fecal fat: FE-1 sensitivity 96%, specificity 88%
      - if low EPI probability (5%), FE-1 false neg = 1.1%, false pos = 11%
      - if high EPI probability (40%), FE-1 false neg = ~ 10%
- Fecal chymotrypsin (less sensitive than FE-1)
- Breath testing via 13-C mixed triglyceride marked substrates (unavailable in US)
- Imaging severity of CP does not correlate with presence or severity of EPI


Differential Diagnosis and Diagnostic Approach to EPI

- Coeliac disease
  - Endoscopic ultrasound, CT, or MRI
- SIPO
  - Hydrogen breath test, stool for IBS
- IBD
  - Endoscopy
- IBS
  - Symptoms
- Colonoscopy
- Microscopic colitis
  - Typically in older women
- Often taking NSAID or PPI
- Colonoscopy, biopsy

**FE-1 in stool**
- Feecal fat determination (qualitative or quantitative)
- Specialized direct pancreatic function tests, if available
- Trial of PERT
**Pancreatic Enzyme Replacement Therapy Corrects Nutritional Deficiencies in Chronic Pancreatitis**

*The Solution to EPI is... Pancreatic Enzyme Replacement Therapy (PERT)*

- PERT to be taken **WITH** meals
- Approximately **36,000-80,000 units of lipase per meal** (half for snacks)
- In a meta-analysis of 17 studies of 511 CP patients, PERT significantly improved coefficient of fat absorption compared to baseline (p<0.00001) and placebo (p=0.0001), and reduced fecal fat excretion
- No significant adverse events with PERT
- PERT improves nutritional parameters, GI symptoms, and quality of life
- High-dose or enteric-coated enzymes more effective than low-dose or non-coated


**Types of Pancreatic Enzyme Replacement Therapy**

**Enteric Coated Capsule**
- Creon®
- Zenpep®
- Pancreaze®
- Ultresa®
- Pertzye®

**Non-Enteric Coated Tablet** (Need PPI Co-Administration)
- Viokace™

- Initial FDA regulations of PERT: 1991
- Actual initiation of FDA regulations/approval: 2004-2010
- Risk: Fibrosing colonopathy
  - If > 2,500 lipase units/kg/meal
  - If > 10,000 lipase units/kg/day

1. We suggest PERT in patients with CP and exocrine pancreatic insufficiency to improve the complications of malnutrition.
2. Patients with CP should have periodic evaluation for malnutrition including tests for osteoporosis and fat-soluble vitamin deficiency.
3. We do not suggest the use of pancreatic enzyme supplements to improve pain in CP.
4. [Pancreatic Enzyme Replacement] Therapy should include an adequate dosage (at least 40,000–50,000 USP units of lipase with each meal) administered during the meal.


Highlights from the 2017 European CP Guidelines...

1. All patients with diagnosis of CP should be screened for EPI
2. Patients with CP should be evaluated annually for EPI
3. Symptoms/nutritional parameters should be followed to assess response to therapy
4. Pancreatic function tests (quantitative fecal fat, acid steatocrit, 13-C breath testing) should be obtained in nonresponders to appropriate PERT dose
5. Treat EPI in pts with symptoms or laboratory signs of malabsorption

PERT Initial Dosing & Adjustment

<table>
<thead>
<tr>
<th>Society Sponsoring Guideline</th>
<th>Year</th>
<th>PERT Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>American College of Gastroenterology [1]</td>
<td>2020</td>
<td>40,000-50,000 units TID with meals (half dose with snacks)</td>
</tr>
<tr>
<td>United European Gastroenterology [2]</td>
<td>2017</td>
<td>40,000-50,000 units TID with meals (half dose with snacks)</td>
</tr>
<tr>
<td>Australasian Pancreatic Club [3]</td>
<td>2015</td>
<td>25,000-40,000 units TID with meals (10,000 units with snacks)</td>
</tr>
</tbody>
</table>

- PERT should be administered with meal (not before or after)
- PERT “non-responders” management:
  - Ensure PERT compliance/correct administration
  - Consider increasing dose
  - Consider adding PPI
  - Consider switching PERT type/formulation
  - Ensure no other comorbid conditions, i.e. SIBO


PERT Treats EPI-Associated Symptoms and Malabsorption in Chronic Pancreatitis

- **Aim:** Evaluate improvement in EPI in patients with CP taking PERT for coefficient of fat absorption (CFA) and clinical symptoms (stool frequency, consistency, abdominal pain & flatulence)

- **Methods:** Post-hoc analysis of 2 double-blind, randomized, placebo-controlled trials of PERT (pancrelipase) x1 week + 51 week OLE in subjects with CP followed by ANOVA analysis for symptoms response calculations.

- **Study Population:**
  - 116 CP patients (59 treated with PERT & 57 with placebo)
  - 86 (74%) men, median age 47 years.

PERT Treats EPI-Associated Symptoms and Malabsorption in Chronic Pancreatitis

- Treatment with PERT vs. Placebo significantly improved stool frequency at week 1 (71.9% vs. 38.2%; p=0.001)

PERT Treats EPI-Associated Symptoms and Malabsorption in Chronic Pancreatitis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>P</th>
<th>P</th>
<th>P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>0.842</td>
<td>&lt;0.001</td>
<td>0.850</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0.285</td>
<td>&lt;0.001</td>
<td>0.058</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stool consistency</td>
<td>0.030</td>
<td>&lt;0.001</td>
<td>0.035</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stool frequency</td>
<td>-0.001</td>
<td>-0.001</td>
<td>-0.001</td>
<td>-0.001</td>
</tr>
</tbody>
</table>

- **Stool Coefficient of Fat Absorption and Mean Stool Fat improved with PERT**
- On ANOVA, improvement in Stool frequency and consistency positively correlated with improvement in CFA and mean stool fat.
- **PERT use did not affect significant changes in abdominal pain & flatulence.**
- **Improved stool frequency and consistency may serve as surrogate clinical markers of response to PERT.**


Consequences of Exocrine Pancreatic Insufficiency

- Nutritional Consequences\(^1\)
  - Deficiencies in fat-soluble vitamins (A, D, E, K) and Vitamin B-12
  - Bone Disease
  - Weight loss
  - Malnutrition
- Impaired quality of life\(^2\)
- Increased mortality in advanced pancreatic cancer\(^3\)
  - If fecal elastase-1 ≤ 20 µg/g, Median survival 7 vs. 11 months, p=0.031
- Substantial weight loss (>10%) worsens pancreatic cancer survival\(^4\)

EPI in Chronic Pancreatitis Is Associated with Increased Risk of Cardiovascular Events

- **Aim:** To evaluate the risk of cardiovascular (CV) events in a CP cohort and evaluate the association with EPI.

- **Methods:** Prospective, longitudinal cohort study of 433 CP patients in Spain (Mean age 47.8 ± 14.4 years of age; 79.1% male; Mean follow-up was 8.6 ± 4.6 years).

**Conclusions:**
- Higher incidence of CV events if EPI present (Incidence Rate Ratio 3.67, 95% CI 1.92-7.24, p<0.001)
- Increased CV risk on Multivariate Analysis if:
  - EPI without DM (OR 4.96; 95% CI 1.68-14.65)
  - Coexistence of EPI and DM (OR 6.54; 95% CI 2.71-15.77)
  - Hypertension (OR 3.40; 95% CI 1.50-7.72)
  - Smoking (OR 2.91, 95% CI 1.07-9.79)


---

EPI in Chronic Pancreatitis Is Associated with Increased Risk of Mortality

- **Aim:** Assess mortality risk of EPI in CP patients

- **Methods:** prospective longitudinal cohort study of 430 CP patients (79.1% M; mean age 47.8 yrs; mean follow up 8.6±4.6 yrs)

**Conclusions:** EPI is associated with increased:
- Mortality (HR 2.59; p<0.003)
- Cirrhosis (HR 3.87; p<0.001)
- Age at diagnosis (HR 1.05; p<0.001)
- Toxic etiology of CP (HR 3.11; p<0.05)
- Respiratory comorbidities (HR 2.19; p<0.03)
- Lower nutritional markers in EPI vs. non-EPI (p<0.001) and in pts who died vs. survived (p<0.001)

Poor Nutritional Status Decreases Overall Survival in Pancreatic Cancer

CONUT Score calculated from serum albumin, total cholesterol, & total lymphocyte count


Anthropomorphic Effects of EPI in CP

**Weight:**
- EPI is associated with being underweight
- On multivariate analysis, presence of EPI was significantly and independently associated with lower BMI

**Muscle Mass:**
- EPI significantly increases risk for sarcopenia
- Presence of sarcopenia also increases risk for EPI (76% of CP pts with sarcopenia had EPI; OR 3.8, 95%CI 1.2-12.5, p=0.003)

Metabolic Bone Disease in CP Patients with EPI

- Decreased bone mineral density is common in CP and increased in those with EPI.1,2
- Pooled Prevalence of Bone Disease in CP (Systematic Review & Meta-Analysis of 513 pts): Osteopenia 40%; Osteoporosis 23%.3
- Osteoporosis is increased in CP compared to matched controls (34% vs. 10%)4
- Low-trauma fractures are common in CP (4.8% Prevalence) and significantly increased (HR 2.0, p<0.0001) compared to matched controls5,6
- Treatment with PERT in CP decreased fracture risk (HR 0.8)6
- Treatment with PERT is associated with significantly improved bone density via DEXA score (p<0.05)7


The Economic Burden of Illness Associated with EPI

- 7,366 patients with EPI on pancreatic enzyme replacement therapy (PERT) matched with a cohort of 22,089 control patients without EPI1

Conclusions:
- Patients with EPI had significantly higher direct healthcare costs than non-EPI controls (p<0.001)
- There were no significant differences in costs due to workplace absence in EPI vs non-EPI controls
- Patients with EPI had significantly higher indirect costs due to short-term disability and long-term disability than non-EPI controls in 12-month follow up period (p<0.001)
- A separate pharmaceutical claims database study of 819 pancreatic cancer pts looking at early PERT initiation (< 3weeks) post-Whipple demonstrated significantly lower total healthcare costs in those receiving PERT vs. no PERT ($96,334 vs. $106,820; p= 0.0348)2

Barriers to EPI Diagnosis

- Average of 3.7 years before pts sought care
- Median of 4 visits before making EPI diagnosis

- Lack of Awareness:
  - 2/3 of Patients haven’t heard of EPI
  - 78% of patients don’t know EPI-associated symptoms
  - **1 in 4 patients was diagnosed with a different condition before EPI diagnosis** (25% for PCP, 24% for GI)

- Communication & Knowledge Improve Care:
  - Gastroenterologists understand EPI (98% have diagnosed a patient with EPI)
  - 78% of PCPs and 92% of GIs surveyed believed EPI symptom patient education should be done by GI
  - 84% of PCPs and 93% of GIs surveyed believed all of most of EPI treatment should be done by GI

Appropriate Use of PERT in Pancreatic Cancer Patients Is Low, But Improves Symptoms & Weight Loss

- **Aim:** To determine frequency of appropriate PERT use in pancreatic cancer & impact on symptom alleviation

- **Methods:** Survey based study of patients in the Pancreatic Cancer Action Network’s Patient Registry of 25 questions about their experience with PERT.

- **Results:**
  - 136 patients: 62 (46%) female; Median age at enrollment 63 (range 23-86)
  - 70% adenocarcinoma, 9% neuroendocrine, & 21% other/unknown
  - 85 (63%) surgery, 59 (43%) radiation therapy, & 112 (82%) chemotherapy

- **PERT Usage:**
  - 84% (115/136) spoke to a healthcare provider about PERT
  - 76% (104/136) were prescribed PERT, of which 65% (68/104) were correctly prescribed PERT
  - Only 44/68 reported compliance with correctly prescribed PERT (32% overall)

**Appropriate Use of PERT in Pancreatic Cancer Patients Is Low, But Improves Symptoms & Weight Loss**

**Symptom Response: PERT with meals vs. prior/after meals:**
- Decreased “Feeling of indigestion” (p=0.005)
- Improved “Increased or foul smelling flatus” (p=0.04)
- Trend to less “Frequent stools,” “Loose stools” & “Visible food particles in stool”
- Trend to more weight gain & less weight loss

**Conclusions:**
- Appropriate PERT prescriptions & Compliance with PERT administration guidelines remains low
- Improvement in symptoms and less weight loss significantly correlated with appropriate use of PERT
- Increase in PC patient and provider education about appropriate PERT usage and administration is warranted


---

**PERT Use in Chronic Pancreatitis and Pancreatic Cancer Remains Suboptimal**

- Nationwide analysis to evaluate appropriate use of PERT in chronic pancreatitis and pancreatic cancer patients
- 37,061 Chronic pancreatitis & 32,461 Pancreatic cancer patients of 48.67 million enrollees in the PharMetrics claims database
- Appropriate PERT use: daily dose of >120,000 lipase units/day.

<table>
<thead>
<tr>
<th></th>
<th>Chronic Pancreatitis</th>
<th>Pancreatic Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tested for EPI</td>
<td>6.5%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Filled Rx for PERT</td>
<td>30.4%</td>
<td>21.9%</td>
</tr>
<tr>
<td>Prescribed Appropriate PERT dose</td>
<td>8.5%</td>
<td>5.5%</td>
</tr>
</tbody>
</table>

- Predictors of PERT use: Number of comorbidities, Testing for EPI, Pancreatic surgery, Duration of enrollment

Pancreatic Cancer-Associated EPI Disparities

- **Aim**: Investigate prevalence of EPI treatment with PERT in Pancreatic Cancer (PC) and factors influencing treatment
- **Methods**: Case control study of PC pts identified using SNOMED-CT coding with and without PERT rx in commercial health record database (Explorys, Inc, Cleveland, OH, USA) using logistic regression.

<table>
<thead>
<tr>
<th>More Likely to Receive PERT Rx</th>
<th>Less Likely to Receive PERT Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian (OR 1.693, p&lt;0.0001)</td>
<td>African-American (OR 0.7281, p&lt;0.0001)</td>
</tr>
<tr>
<td>Age &lt; 65 (OR 1.204, p&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Non-smoker (OR 2.6894, p&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Cannabis user (OR 2.067, p&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Hx of Chronic Pancreatitis (OR 2.9572, p&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Malnutrition (OR 2.4592, p&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Hx of Bariatric Surgery (OR 2.1705, p&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Vitamin D Deficiency (OR 2.057, p&lt;0.0001)</td>
<td></td>
</tr>
</tbody>
</table>

- **Conclusion**: EPI in PC remains undertreated, disproportionately affecting older and African-American patients.

Disparities in Chronic Pancreatits-Associated EPI

- **Aim**: Investigate prevalence of EPI treatment with PERT in Chronic Pancreatitis (CP) and factors influencing treatment
- **Methods**: Case control study of CP pts identified using SNOMED-CT coding with and without PERT rx in commercial health record database (Explorys, Inc, Cleveland, OH, USA) using logistic regression.

<table>
<thead>
<tr>
<th>More Likely to Receive PERT Rx</th>
<th>Less Likely to Receive PERT Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian (OR 1.55, p&lt;0.0001)</td>
<td>African-American (OR 0.91, p&lt;0.01)</td>
</tr>
<tr>
<td>Tobacco Smoker, Cannabis User (p&lt;0.0001)</td>
<td>Hispanic (OR 0.91, p&lt;0.01)</td>
</tr>
<tr>
<td>Hx of Pancreatic Cancer (OR 1.83, p&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Vitamin D Deficiency (OR 1.46, p&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis (OR 1.48, p&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Malnutrition (OR 1.9, p&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Hx of Bariatric Surgery (OR 1.40, p&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td>Hx of Celiac Disease (OR 1.50, p&lt;0.0001)</td>
<td></td>
</tr>
</tbody>
</table>

- **Conclusion**: EPI in PC remains undertreated, with significant treatment disparities affecting African-American and Hispanic patients.
Pancreatic Specialty Centers Have Improved Rates of Treatment of EPI in Chronic Pancreatitis

Overall EPI Treatment Rate 15.8% Nationwide

NPF-C: National Pancreas Foundation Center of Excellence


PERT Use in Unresectable Pancreatic Cancer

• Aim: Assess the effect of PERT use on BMI in unresectable Pancreatic Cancer

• Methods: open label RCT of PERT in 88 patients in Japan with unresectable pancreatic cancer to assess BMI at 8 weeks (1ry endpoint), other nutritional markers (2ry), and survival (2ry)

Results:
• Change in BMI at 8 weeks: No significant difference (p=0.780)
• Other nutritional markers comparable in PERT vs. no PERT

Survival:
• Median Overall Survival: PERT 19 months (95%CI 14-22mon) vs. No PERT 12 months (95%CI 8-17mon) (p=0.070)
• 1-Year Survival: PERT 73.0% vs. No PERT 49.4%

Case Wrap-Up

- Treatment for EPI with PERT was started
- Bloating and abdominal pain improved
- Steatorrhea resolved
- He gained back 5 pounds
- Vitamin D supplemented and normalized
- CA 19-9 remains normal
- He remains in an active imaging screening program for pancreatic cancer
- He is following with endocrinology for management of diabetes

Exocrine Pancreatic Insufficiency: Take Home Points

- EPI is common in Chronic Pancreatitis as well as other diseases
- EPI may present with increased stool frequency and decreased stool consistency amongst other maldigestive symptoms
- EPI is treated with PERT, but barriers to care and undertreatment remain
- Untreated EPI has substantial impact on symptoms, quality of life, morbidity, and mortality
Acknowledgements

• Thank You!!

National Pancreas Foundation Center of Excellence at the University of Miami

Questions?

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Jodie A. Barkin, MD

Moderator:
C. Roberto Simons-Linares, MD
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