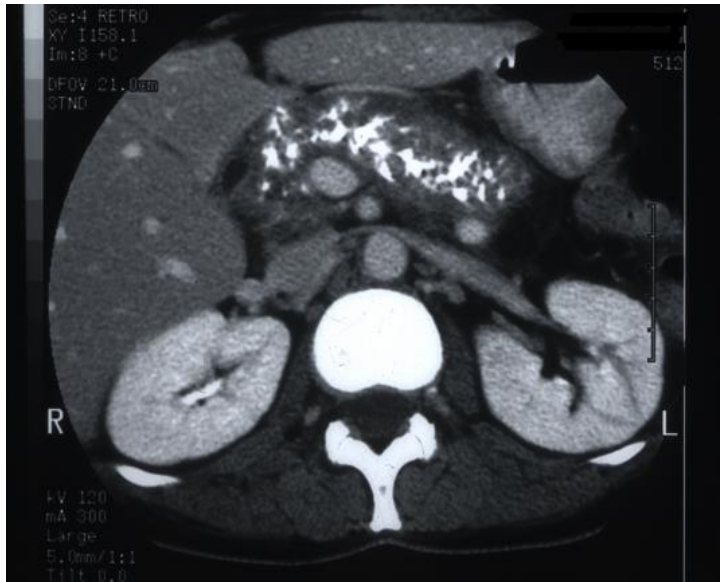
Exocrine Pancreatic Insufficiency Treatment
The known and the unknown



Chris E. Forsmark, M.D.

UFHealth
UNIVERSITY OF FLORIDA HEALTH

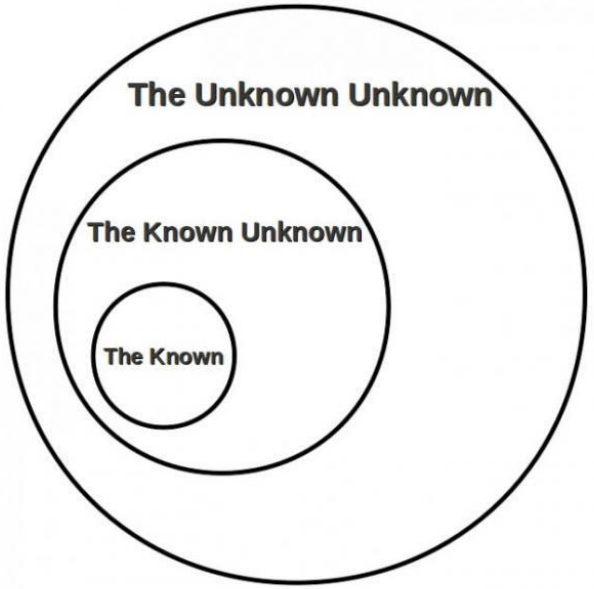
A patient of mine

- 26 year old woman
- TPIAT 9 years ago for relapsing pancreatitis, CFTR/SPINK mutations
- On low dose insulin
- Does not take any PERT. Took for a while but stopped years ago
- Weight stable, no steatorrhea or diarrhea, normal fat soluble vitamin levels, quite active and fully employed, DEXA normal
- Eats 6 small meals daily (by choice), not vegan but relatively low fat

What would you recommend to her now?

Some conundrums to ponder

- What do we actually mean when we say the pancreas is insufficient?
- How do we know who needs treatment for insufficiency?
- What is the most effective treatment strategy?
- How do we know if treatment is working?
- Are there special situations where we need to change our strategy?
- If we know what to do, do we actually do it?

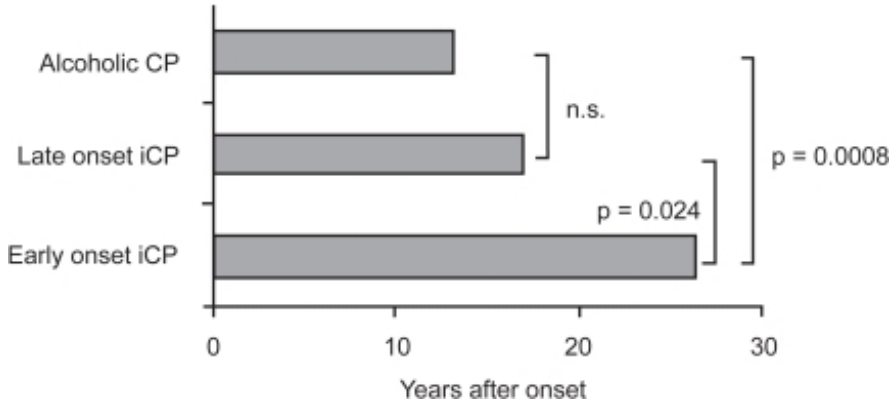


What is exocrine pancreatic **insufficiency**?

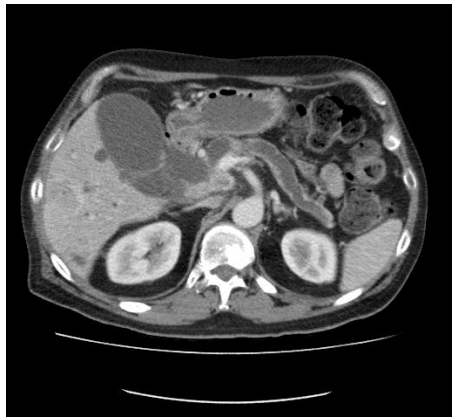
- Diminished pancreatic digestive enzyme delivery to the intestine?
  - Less than stimulated physiologic maximum? (Direct PFT)
  - Less than needed for meal digestion and absorption? (test meal, 72 hour fecal fat)
  - Less than ”average” ? (random fecal elastase)
- Insufficient pancreatic digestive enzymes in the intestine to accomplish **normal** digestion of a meal? Or a **minimally sufficient** digestion of a meal?
  - Humans have multiple compensatory mechanisms for digestion and absorption- protein, carbohydrates, and even fat
  - The pancreas has a large functional reserve
  - Under “normal” circumstances humans don’t digest and absorb all dietary nutrients
- What meal are we talking about? High fat, low fat, large, small,……..
- What nutritional or clinical consequences define insufficient?
  - Steatorrhea with some meals
  - BMI, muscle mass, steatorrhea, fat soluble vitamin deficiency, bloating and gas, …….

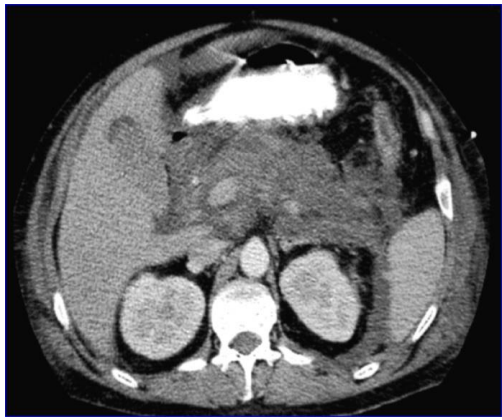
Exocrine pancreatic insufficiency

- Chronic pancreatitis
  - ≅ 200,000 prevalence, 30-50% EPI
  - Duration affects risk
  - Etiology impacts risk: alcohol, smoking, genetics
- Cystic fibrosis
  - ≅ 30,000 prevalence
- Pancreatic resection
  - ≅ 15,000 yearly
- Pancreatic cancer
  - ≅50,000 yearly
- Pancreatic duct obstruction
  - Benign or malignant
- Schwachman-Diamond and Johanson-Blizzard
- Isolated individual enzyme deficiencies
- Necrotizing pancreatitis



Layer P et al, 1994

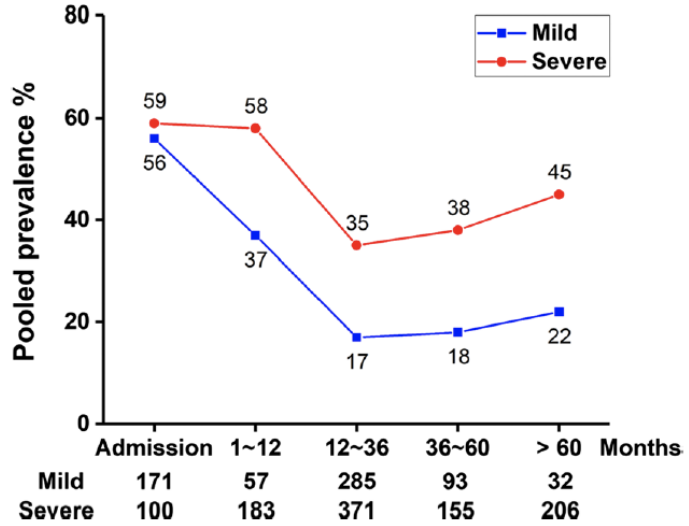




Exocrine pancreatic insufficiency?

- Acute pancreatitis or RAP without necrosis
- Diabetics
- The aged
- Renal failure
- Asynchrony after surgery
- NASH
- ZE

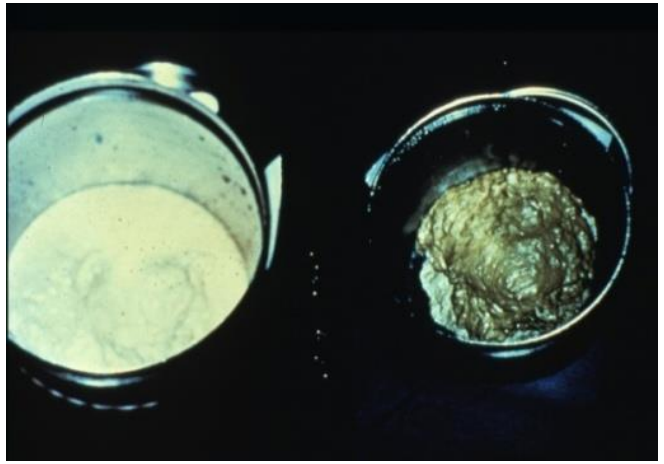
- Malnourished
- IBS
- Critically ill
- Celiac disease and other mucosal diseases (IBD)
- Osteoporosis
- Smokers
- Bloating, dyspepsia, gas, the internet

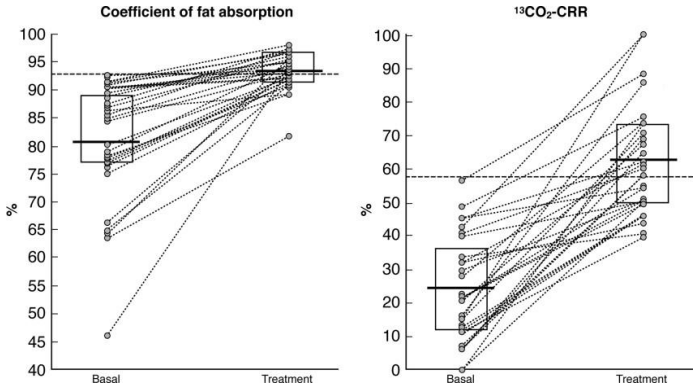


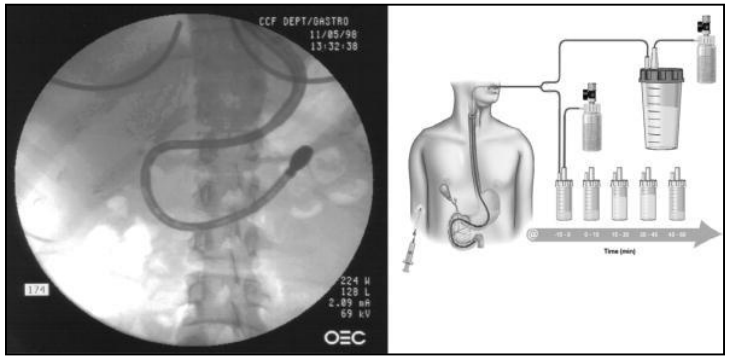
Huang W 2019

Diagnosis of EPI

- Measure fat maldigestion or malabsorption
  - Quantitative or qualitative
- Measure pancreatic enzyme-specific fat digestion
  - Test meal, breath tests, blood tests
- Measure pancreatic enzyme output
  - Tube based
  - Stool collection







Fecal elastase

- Not actually elastase (chymotrypsin-like elastases: CELA3A/B
- Fecal elastase < 200 µg/gm stool (or < 100?)
- Less accurate in children
- In a systematic review and meta-analysis of 14 studies, 1,100 patients
  - Compared to PFT
    - sensitivity 0.77 (95% CI 0.58-0.89) and specificity 0.88 (0.78-0.93)
  - Compared to abnormal fecal fat
    - sensitivity 0.96 (0.79-0.99) and specificity 0.88 (0.59-0.97)
  - In a low prevalence population (<5%) **false positive rate** 11%

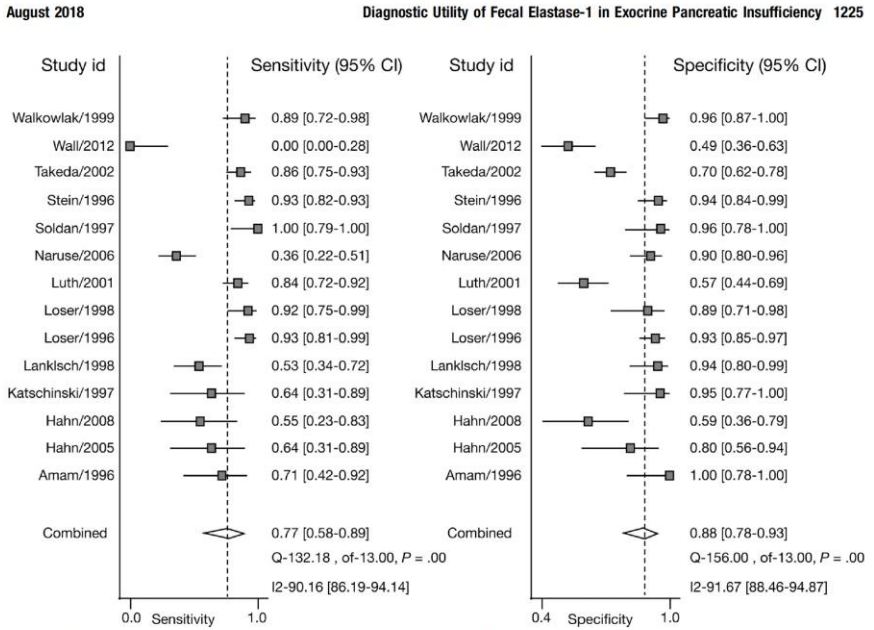


Figure 2. Forest plot showing study-specific and mean sensitivity and specificity of FE-1 compared with secretin stimulation test for exocrine pancreatic insufficiency with corresponding heterogeneity statistics.

Vanga RR et al. Clin Gastroenterol Hepatol 2018, Benini L, et al. Pancreatology 2013

Fecal elastase- many caveats

- Stool sample must be solid or semi-solid
  - Watery stool dilutes elastase
- Test does not require patients stop pancreatic enzyme therapy
  - Enzymes are porcine in origin, test measures human CELA3A/B
- Worth testing more than once as variable
- A low elastase alone does not prove EPI is present
  - Correct clinical setting, correct symptoms
  - Be aware of potential of age and DM to affect result
- Fecal chymotrypsin is also available but FAR less accurate then elastase

Is there expert consensus on approach?

- Best cut-off for diagnosis of EPI?
  - FE1 < 500: 5%
  - FE1 < 200: 59%
  - FE1 < 100: 18%
  - FE1 < 50: 4%
- Does level of FE1 influence initial PERT dose?
  - No: 77%
- Case vignettes- significant disagreement

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Diagnosis and treatment of exocrine pancreatic insufficiency in chronic pancreatitis: An international expert survey and case vignette study

Florence E.M. de Rijk [a, b, *], Charlotte L. van Veldhuisen [b, c], Marc G. Besselink [c], Jeanin E. van Hooft [d], Hjalmar C. van Santvoort [e, f], Erwin J.M. van Geenen [g], Peter Hegyi [h, i], J-Matthias Löhr [j], Juan E. Dominguez-Munoz [k], Pieter Jan F. de Jonge [a], Marco J. Bruno [a], Robert C. Verdonk [l], for the Dutch Pancreatitis Study Group

Consequences of exocrine insufficiency: who needs treatment?

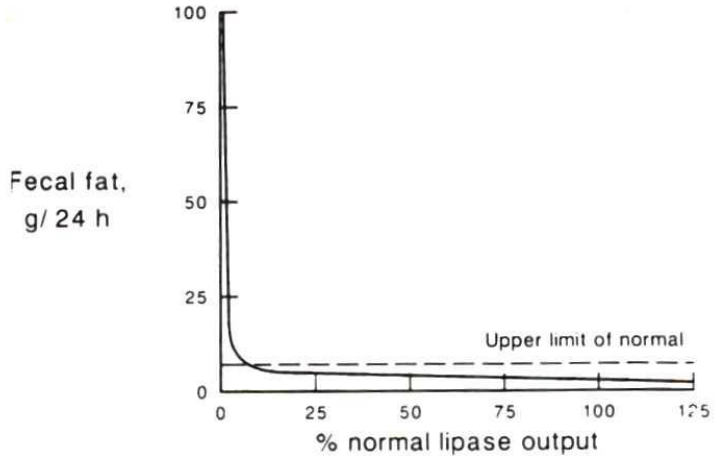
- None detectable
- Steatorrhea (but often not diarrhea)
- Weight loss
- Difficulty in managing concomitant diabetes (Type 3c)
- Osteopenia and osteoporosis, bone fracture
- Specific vitamin, mineral or micronutrient deficiency
  - Calcium and vitamin D
  - Other fat soluble vitamins (A,K,E)
  - Mg, zinc, folate, essential fatty acids
  - Other vitamins?
- Excess mortality (CP and PDAC)

Baseline studies and interventions

- Anthropometrics
  - BMI
  - Muscle mass or strength
    - CT of psoas muscle at L3 level
    - Handgrip strength
- Basic nutritional parameters
  - Prealbumin, retinol binding protein
- Vitamin D, A, E level, INR
- B vitamins, folate
- HgB A1c
- DEXA scan
  - Only 1 in 5 get one (Pancreatology 2020;20:1109)
- Smoking cessation referral
- Alcohol abstinence referral
- Lifestyle parameters (physical activity)

Principles of therapy for exocrine insufficiency

- Accurate diagnosis
- Need approximately 90,000 USP units of lipase per meal (= 10% of normal output per meal)
  - The normal pancreas produces > 10,000 U/kg/meal
  - PERT does not work as effectively as normal output
  - Exogenous and endogenous lipase
    - Minimum starting dosage 40,000-50,000 with each meal and half as much with snacks
    - Can weight-base dose for pediatrics or for those < 160 pounds
  - Must be delivered **during** the meal
- Measure and supplement fat soluble vitamins
- Measure bone density



Enzyme formulations in US

Product	Formulation	Lipase content/capsule or pill
Creon®	Enteric-coated porcine	3000, 6000, 12000, 24000, 36000
Pancreaze®	Enteric-coated porcine	2600, 4200, 10500, 16800, 21000
Zenpep®	Enteric-coated porcine	3000, 5000, 10000, 15000, 20000, 25000, 40000
Pertzye®	Enteric-coated porcine with bicarbonate	4000, 8000, 16000, 24000
Viokace®	Non-enteric coated porcine	10440, 20880

Well established high risk groups

- Chronic pancreatitis
- Pancreatic surgery
- Pancreatic cancer and IPMN
- Cystic fibrosis
- A few others

Are they prescribed PERT?

- At correct dosage and timing?

Are they taking PERT?

- Cost?
- Noncompliance?

Is PERT effective?

Are they being monitored or treated for osteoporosis or other metabolic consequences?

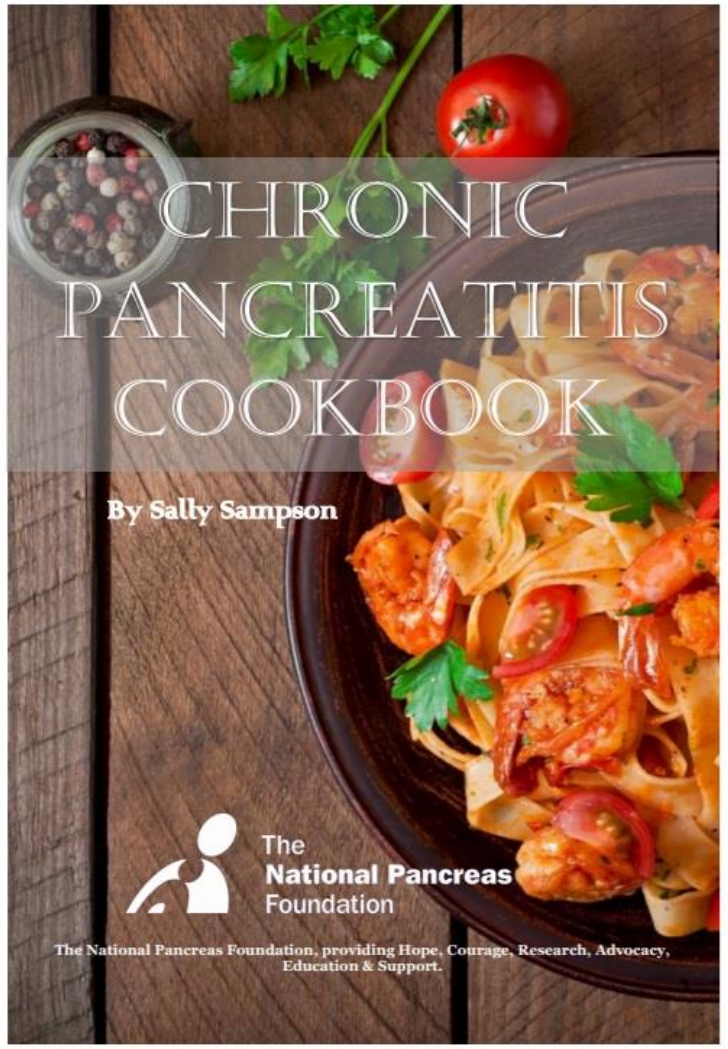
PERT usage in the US in Chronic Pancreatitis

- 37,061 insured patients with chronic pancreatitis in US (2001-2013)
- 6.5% had any test for EPI (elastase, fecal fat, etc)
- 30.4% received prescription for PERT
- 31% of those received minimally appropriate dosage ($\geq$ 40,000/meal) after diagnosis ($\cong$10% overall)

Aliment Pharmacol Ther 2020;51:958-67

Dietary recommendations and EPI

- Numerous recommendations, usually low-fat or very low fat
- Many also recommend multiple small meals
- Avoid the very low fat diets ➡ fat soluble vitamin deficiency
- MCT oil often mentioned but almost never needed
- Everyone needs calcium and vitamin D



Is treatment working? Measurement of efficacy

What is useful?

- Clinical response
  - Visible steatorrhea
  - Strength, energy, etc
- Anthropometrics
  - Muscle strength
- Normalizing fat soluble vitamin levels
- Normalizing retinol binding protein

What is generally not helpful?

- Fecal fat measurement
- Fecal elastase
- Non-specific symptoms
  - Bloating
  - Dyspepsia
  - Gas

Failure to respond to PERT

- Inadequate dosage
  - 1/3 of prescriptions never filled
  - Expensive
- Wrong timing
- Acid inactivation of non-enteric coated preparation

Alternative diagnosis

- SIBO
- Pancreatic cancer
- Other malignancy
- Celiac disease

Special circumstances

- Pediatrics
  - 2-4,000/4 oz formula or breast milk
  - 1000/kg/meal age < 4
  - 500/kg/meal age > 4
- Tube feeds
  - Elemental/semi-elemental
  - Relizorb-immobilized lipase
- Supplements
  - Encala
  - ~~MCT oil~~

Summary

- EPI is common in patients with chronic pancreatitis (and pancreatic cancer and pancreatic resections)
  - In chronic pancreatitis, duration, etiology and concomitant smoking affect risk
  - Few patients are tested for EPI, and few receive PERT therapy
- EPI can be seen in a variety of other conditions, with previous acute pancreatitis being most common
- There is no widely available and accurate diagnostic test for EPI
  - Clinical suspicion and fecal elastase are the best we have and these are inaccurate

Summary

- Once a diagnosis of EPI is made, baseline nutritional parameters should be obtained, and therapy begun using a starting dosage no less than 40,000-50,000 USP units of lipase during each meal, and ½ with snacks
- Determine efficacy based on clinical features, and improvement in nutritional measures. Increase dosage up to 90,000 USP units of lipase during each meal, and ½ with snacks (or occasionally more)
- Assess for osteoporosis and osteopenia, and treat if present
- Non-responders are usually either due to inadequate dosage or wrong timing

Thank you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