Carol Rees Parrish, MS, RDN, Series Editor

50 Ways to Treat Pancreatic Insufficiency (ok, maybe not 50…)

Valaree Williams

Patients with exocrine pancreatic insufficiency (EPI) are at risk for malnutrition and other life-altering complications resulting from malabsorption. Unfortunately, due to a similar presentation as other digestive disorders and a lack of simple, effective testing, EPI is often underdiagnosed. When diagnosed, EPI may be inadequately treated. This review explores the nuances of diagnosing and treating EPI and discusses treatment options including, and beyond, pancreatic enzyme replacement therapy.

INTRODUCTION

Exocrine pancreatic insufficiency (EPI) is the inability of the pancreas to produce or secrete pancreatic enzymes and bicarbonate for action in the intestine to achieve normal digestion and absorption. EPI can be caused by changes in the digestive process in which the exocrine pancreas is involved including alterations in pancreatic stimulation, pancreatic enzyme synthesis, transport of pancreatic secretions, and synchronization of gastrointestinal secretions.[1] Risk factors for EPI can be divided into pancreatic and extra-pancreatic disorders that include chronic pancreatitis, cystic fibrosis, and pancreatic cancer, as well as altered surgical anatomy including pancreatoduodenectomy and gastrectomy (see Table 1). If unmanaged, the maldigestion resulting from EPI can lead to malnutrition, micronutrient deficiencies, sarcopenia, osteopenia/osteoporosis, and decreased quality of life.[2]

EPI is often underrecognized and may be misdiagnosed as other gastrointestinal diseases, hence, delay in treatment is common. The diagnosis of EPI is complicated by the lack of accurate, easy-to-perform diagnostic tests and requires the evaluation of symptoms and nutritional markers combined with a non-invasive pancreatic function test. The current prevalence of EPI is unknown due to the wide range in etiologies and, as a result, often goes untreated.[1] Timely identification and treatment of EPI are necessary due to the disease's impact on nutrition status, risk of comorbidities, and quality of life.[1] Additionally, it may be beneficial to educate patients with a high risk of EPI (such as patients with pancreatic cancer), about classic signs and symptoms associated with EPI to facilitate a timely diagnosis and initiation of treatment. It is critical

Valaree Williams, MS, RD, CSO, LDN, CNSC, FAND Clinical Oncology Nutritionist, American Oncology Network, Philadelphia, PA

Table 1. Pancreatic and Extra-pancreatic Causes of EPI [1,26,27]

Pancreatic Disorders
♦ Acute pancreatitis • Especially with extensive pancreatic necrosis • Repeated bouts of acute pancreatitis
♦ Chronic pancreatitis • Toxic-Metabolic ○ Includes alcohol misuse and tobacco smoking ○ High users include head and neck cancer patients; need to query not only, do you drink alcohol, but also, did you ever drink alcohol, and if so, how long and how much[28]
♦ Trauma
♦ Medications
♦ Genetic • Includes hypertriglyceridemia
♦ Autoimmune
♦ Recurrent acute or severe acute pancreatitis
♦ Obstructive • Includes pancreatic divisum and widespread pancreatic calcifications
♦ Cystic fibrosis
♦ Pancreatic cancer (especially tumors in pancreatic head)
♦ Pancreatic atrophy after allogeneic hematopoietic cell transplantation
♦ Main pancreatic duct obstruction
♦ Pancreatic atrophy due to immunotherapy
♦ Idiopathic
Pancreatic or Other Surgeries
♦ Pancreatic surgery
♦ Gastrointestinal surgery including: • Esophagectomy • Gastrectomy • Roux en y gastric bypass • Gastrojejunostomy • Proximal bowel resection
Extra-Pancreatic Disorders
♦ Celiac disease
♦ Inflammatory bowel disease
♦ Type 1, 2 and 3c diabetes
♦ Treatment with somatostatin analog
♦ HIV
♦ Cirrhosis

for clinicians to consider EPI in the differential diagnosis, particularly for patients at high risk for the condition (see Table 1).

Determining the Presence of Exocrine Pancreatic Insufficiency

The diagnosis of EPI is a challenging process that requires a clinician to:

1. identify the patient at risk for EPI
2. evaluate with a thorough review of signs and symptoms of malabsorption and maldigestion
3. assess indicators of malnutrition
4. obtain noninvasive pancreatic function test/s.

The combination of at least two of the three criteria (signs and symptoms, indicators of malnutrition and noninvasive pancreatic function tests) can be considered sufficient to diagnose EPI and initiate appropriate treatment.[1] Noninvasive pancreatic function tests are more helpful to determine the presence of EPI in those conditions not as commonly associated with it such as celiac disease, inflammatory bowel disease, and diabetes.[1]

Signs and Symptoms

The maldigestion and malabsorption produced by EPI can result in a variety of signs and symptoms (see Table 2). Overt symptoms of EPI may not be present in early-stage EPI and may be influenced by other conditions and treatments including slow gut motility and use of opioid medications.[3] Additionally, patients may self-regulate their diet to manage and lessen symptoms of EPI, therefore a connection between dietary intake and symptoms is a necessary part of the work-up.[4]

It can be difficult to separate signs and symptoms of EPI from those related to other diseases and treatments. To effectively evaluate symptoms, a clinician needs to ask focused and detailed questions regarding EPI symptoms and allow adequate time for assessment during patient visits. EPI symptom checklists can be helpful to guide these discussions and support at-home symptom monitoring. See Table 3 for tools to track EPI symptoms and guide conversations to identify EPI.

Testing

Several direct and indirect methods for the evaluation of exocrine pancreatic function are available (see Table 4). Direct methods offer high sensitivity and specificity, but routine usage in clinical practice is limited by the lack of availability, invasive nature, and expense. Direct methods include the quantification of duodenal secretions collected via probe or endoscopy after stimulation.[2,5] Indirect methods measure the metabolites derived from the action of pancreatic enzymes and offer a less sensitive, lower cost and easier-to-implement option.[5] These methods are more commonly used in the clinical setting. A non-invasive pancreatic function test is recommended to aid in EPI diagnosis, especially in the absence of

Table 2. Symptoms of EPI[2]

- Steatorrhea (stools may be bulky, pale, foul smelling, greasy/oily/foamy or float)
- Abdominal bloating
- Postprandial abdominal pain or cramping
- Loose stools
- Frequent or urgent stools, especially after meals
- Flatulence (may be malodorous)
- Indigestion
- Weight loss despite adequate caloric intake

clinical symptoms or with more uncommon causes of EPI. Testing may not be needed in patients with conditions known for a high prevalence of EPI including severe chronic pancreatitis, cystic fibrosis, pancreatic head destruction from either tumor or episode of acute pancreatitis, or after total pancreatectomy.

Imaging

Imaging, including ultrasound, magnetic resonance imaging, or computed tomography, may reveal atrophy of the pancreas or the presence of calcifications. Pancreatic atrophy or calcifications are associated with EPI and should lead to further evaluation in patients with these findings on imaging.[6]

Options for Treating Exocrine Pancreatic Insufficiency

Pancreatic Enzyme Replacement Therapy

Pancreatic enzyme replacement therapy (PERT) is the primary management strategy for EPI. PERT is the use of prescription pancreatic enzymes (pancrealipase) taken with all meals, snacks, and fat-containing oral nutrition supplements to mimic pancreatic exocrine function by providing amylase, lipase, and protease. PERT aims to correct maldigestion and malabsorption by providing adequate enzymatic activity into the small intestine in conjunction with gastric emptying.[6] PERT efficacy is dependent on enzymes mixing with the food, emptying from the stomach with the food, appropriate duodenal pH, mixing with duodenal chyme and bile acids, and finally rapid release of PERT in the duodenum (which is pH dependent). With adequate PERT use to manage maldigestion, dietary fat restriction is not necessary.

Currently, porcine-derived enzymes are the only prescription PERT product available in the United States. As a clinician, it is important to be transparent with patients regarding the source of prescription PERT products due to potential issues in patients with a pork allergy or cultural or religious beliefs limiting the use of porcine-derived products. Prescription pancreatic enzymes are available in non-enteric coated tablets and delayed-release capsules filled with enteric coated beads, microtablets, or spheres (see Table 5). Formulation selection may be influenced by cost and insurance coverage. Patients benefit from delayed-release capsules as the enteric coating of the beads, microtablets, or spheres protect the enzymes from being denatured by gastric acid and allow for appropriate activation of the enzymes in the alkaline environment of the small intestine.[7] Non-enteric coated tablets paired with a proton pump inhibitor or opening the delayed-release capsules and sprinkling on non-dairy soft food such as applesauce, is recommended for those with accelerated gastric emptying and in those with gastric reducing surgeries (Roux-en-Y gastric bypass, distal gastrectomy, etc.).[3] If delayed-release capsules are opened for administration, the enteric

Table 3. Signs and Symptoms Checklists and Conversation Guides

Symptom Checklists

Checklists to provide to patients to assist in a thorough evaluation of EPI symptoms

- American Gastroenterological Association EPI Symptom Tracker
  - https://cdn.coverstand.com/61781/632191/108ce8f53c55b918f459258a510612926bf06f49.pdf
- AbbVie Pharmaceuticals Exocrine Pancreatic Insufficiency (EPI) GI Symptom Tracker
  - https://www.identifyepi.com/content/dam/identifyepihcp/pdf/gi-symptom-tracker.pdf

Conversation Guide

Provides questions and information to help clinicians navigate evaluation and diagnosis of EPI

- AbbVie Pharmaceuticals Health Care Provider EPI Conversation Guide
  - https://www.identifyepi.com/content/dam/identifyepihcp/pdf/hcp-epi-conversation-guide.pdf

Table 4. Common Diagnostic Tests for EPI [1,4,5,13]

Direct Tests			
Tests	**Results**	**Advantages**	**Limitations**
Secretin Pancreatic Function Test	Abnormal: bicarbonate concentration <80 mM/L at 60 minutes	• High sensitivity and specificity	• Invasive procedure • Requires anesthesia and endoscopy • Expensive • Availability often limited to specialized centers
Cholecystokinin-stimulated Pancreatic Function Test	Abnormal: peak lipase of <780,000 IU/L	• High sensitivity and specificity	• Invasive procedure • Requires anesthesia and endoscopy • Availability often limited to specialized centers
Indirect Tests			
Coefficient of Fat Absorption (24, 48, 72-hour collection)	Normal: 2 to 7 grams per 24 hours of stool Abnormal: >7 grams of fat per 24 hours of stool	• Gold standard of indirect tests • Compares fat intake versus fat output to demonstrate extent of malabsorption • Useful to monitor EPI treatment efficacy and compliance	• Requires controlled dietary fat intake of 100 grams fat/day and careful evaluation of fat intake • Diet may increase unpleasant EPI symptoms • Cumbersome to perform • Any stool loss can skew results
Qualitative Fecal Fat Test	Positive result showing fat in the stool indicates malabsorption	• Simple and only requires one small stool sample • Must ingest fat; no guideline for amount	• Positive result is unable to determine the extent of malabsorption • Negative result does not definitively rule out malabsorption due to variability in diet and stool samples
Fecal Elastase Concentration (FE-1)	Pancreatic insufficiency: <200 ug/g Severe pancreatic insufficiency: <100 ug/g	• Most widely used test in clinical practice • Simple, non-invasive and does not require ongoing stool collection • No dietary interventions required • Results not impacted by use of PERT	• Lack of consensus regarding cutoff point for EPI diagnosis • Low sensitivity in mild EPI cases • Watery stools or intestinal inflammation can cause false-positive results • Results unreliable after pancreatic resection • Not an effective measure to evaluate benefit of PERT
Carbon 13-Labeled Mixed Triglyceride Breath Test	Pancreatic insufficiency: low CO2 production	• Useful to monitor EPI treatment efficacy and compliance • Increased sensitivity for mild EPI as compared to other tests	• Values affected in patients with intestinal malabsorption, liver disease and/or respiratory disease • Lengthy 6-hour exam administration time
Fecal Chymotrypsin	Pancreatic insufficiency: <3 units/g	• Inexpensive • Useful to monitor EPI treatment efficacy and compliance	• Unreliable for identifying mild EPI • Levels can be low in small bowel mucosal diseases and in patients with low fecal pH
Serum trypsinogen	Pancreatic insufficiency: 20-29 um/mL Severe pancreatic insufficiency: <20 um/L	• Serum test	• Low sensitivity in mild EPI cases • Elevated levels can occur in patients with acute pancreatitis, diabetes mellitus, or renal failure • Not validated in older adults or patients with diabetes mellitus

coated beads should be sprinkled on a spoonful of non-dairy, acidic food that does not require chewing. Non-dairy foods are necessary as the alkaline nature of dairy foods can prematurely activate the microspheres. Soft foods that do not require chewing are recommended to avoid mouth irritation.

The benefits of PERT have been established in multiple populations. Improvements in the coefficients of fat and nitrogen absorption, as well as EPI symptoms were demonstrated in patients with EPI due to chronic pancreatitis or pancreatic surgery.[8] A meta-analysis showed that PERT improved the coefficient of fat absorption, clinical symptoms, and quality of life of patients with chronic pancreatitis and EPI.[9] PERT usage in patients with advanced pancreatic cancer was associated with both a survival benefit and improved quality of life.[10] A randomized controlled trial reported improved nutritional status and quality of life in patients using PERT after gastrectomy for gastric cancer.[11]

A common pitfall of PERT is inadequate dosing. With EPI presenting in infancy through adulthood, PERT is available in various dosages. Some low dosage options are intended for use in pediatric populations but are mistakenly prescribed to adults, resulting in a dosage that is too low to be effective in the treatment of EPI in adults.[12] The common monikers "less is more" and "start low and work up" can result in inadequate PERT dosing leading to inadequate or no improvement in EPI symptoms and increasing frustration for the patient and the clinician. Dosing methods include meal-based, weight-based, and per-gram-of-fat consumed dosing. Common dosing recommendations for an average-sized adult is to begin with 40,000-50,000 units of lipase per meal and 20,000-25,000 units of lipase per snack.[13] Higher dosing of 75,000 units of lipase per meal may be required for patients with EPI due to pancreatic cancer or after gastrointestinal or pancreatic surgery due to anatomic alterations resulting in altered gastrointestinal transit.[2] The dose should be progressively increased until symptoms are sufficiently controlled. PERT dosing needs to be increased with higher energy or higher fat meal intake, reinforcing the importance of understanding a patient's dietary pattern. In addition to adequate PERT dosing per meal, provision of an adequate supply of PERT to take with snacks and oral nutrition supplements is also necessary to promote optimal digestion of all intake. If more than one capsule is required per meal or snack, dosing can be divided throughout the meal by taking part of the dose at the beginning of the meal and distributing the remainder throughout the meal to promote an adequate supply of enzymes for all food consumed.[14]

Treatment of EPI with PERT is not without its challenges. Inadequate dosing and patient non-compliance with PERT can lead to suboptimal results. To promote compliance, time should be given to patient education regarding the causes and symptoms of EPI as well as the role of PERT. Routine follow-up should be scheduled after PERT initiation to allow for dose titration and additional education. If EPI continues despite dose and usage optimization, the addition of a proton pump inhibitor is recommended to promote the necessary alkaline environment for enzymatic function.[1] If EPI continues despite the above interventions, it is necessary to rule out other contributors including small intestinal bacterial overgrowth.

Low-fat Diet

Although a liberal diet with adequate PERT use to promote digestion and absorption is commonly recommended, a low-fat diet may be utilized as a treatment for EPI. This may be due to patient preference or an individual patient's intolerance to PERT. With a low-fat diet to promote improved EPI symptoms, fat intake should be limited to 25 grams per day for patients with severe steatorrhea.[15] Daily fat intake goals should be individualized based on the degree of steatorrhea and change in symptoms

Table 5. Pancreatic Enzyme Replacement Therapy Products Approved by the Food and Drug Administration [21-25]

Type	Brand	Available Strengths (lipase USP units)	Manufacturer
Enteric Coated			
Delayed-release capsule with enteric-coated beads, microtablets, or spheres	Creon	3,000 6,000 12,000 24,000 36,000	AbbVie
	Pancreaze	2,600 4,200 10,500 16,800 21,000 37,000	Vivus
	Zenpep	3,000 5,000 10,000 15,000 20,000 25,000 40,000	Nestle Health Science
Delayed-release capsule with enteric-coated beads, microtablets, or spheres and bicarbonate buffer	Pertzye	4,000 8,000 16,000 24,000	Digestive Care, Inc.
Non-enteric coated			
Tablet, no enteric coating	Viokace	10,440 20,880	Nestle Health Science

with reduced fat intake. The appropriateness of a low-fat diet as treatment for EPI should be determined on a patient-by-patient basis including assessing the patient's ability to consume adequate intake while following a low-fat diet.

Successful implementation of a low-fat diet to manage EPI requires the involvement of a Registered Dietitian Nutritionist to perform a thorough nutrition assessment and develop appropriate, individualized interventions. A thorough understanding of a patient's typical eating pattern is necessary to inform advice regarding foods to choose or increase, as well as promote adequate nutrient intake. To avoid essential fatty acid deficiency, fat sources consumed should be high in essential fatty acids, including corn, sesame, safflower and soybean oils and spreads like sunflower seed butter and mayonnaise and margarine made with soybean oil.[16] Additionally, it is necessary to monitor and ensure adequate intake of fat-soluble vitamins and recommend supplementation as needed.

For patients struggling to consume adequate calories while following a low-fat diet, medium-chain triglycerides (MCT) can be utilized to supplement intake. MCT oil can be substituted for other fats as MCTs do not require enzymatic action or bile salts for digestion or absorption and absorption occurs via passive diffusion along the

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gastrointestinal tract into the portal system bound to albumin.[17] A tablespoon of MCT oil contains 14 grams of fat and 115 calories. Fat from MCT oil should not be counted into the allowed grams of fat per day on a low-fat diet unless too much is used, overwhelming the receptors along the intestinal mucosa. A slow introduction and gradual titration of MCT oil is necessary due to potential gastrointestinal distress including diarrhea, vomiting, nausea, stomach discomfort and intestinal gas.[17] Additionally, compliance can

Table 6. Reasons for Treatment Failure with PERT[1]

Cause	Issue	Action
PERT Order	Inadequate dosing	• Adjust dosing and order to provide PERT for all meals, snacks, and oral nutrition supplements
	Dosing not adequately ordered to cover meals, snacks, and oral nutrition supplements	
	Pt unable to obtain adequate, ongoing supply due to high out-of-pocket cost	• Determine preferred PERT brand of patient's insurance and address any required prior authorization needs • Utilize co-pay assistance and patient assistance programs offered by pharmaceutical companies to assist with cost
Patient Compliance	Inconsistent use with meals, snacks, and oral nutrition supplements	• Re-educate patient on role and appropriate use of PERT • Increase dosage of capsule as needed if patient reports pill burden as cause of non-compliance
	Not taking number of capsules prescribed	
	Inappropriate timing of medication administration (not taking at start and spreading capsules out throughout the meal/snack)	
PERT Activity	Inadequate alkaline environment in small intestine to promote enzymatic function	• Add proton pump inhibitor
	Rapid gastrointestinal transit	• Open capsules or change to non-enteric coated tablet
	Inadequate mixing of enzymes with food throughout the meal with use of higher dose PERT capsules/ tablets	• Change dose of PERT to smaller doses (i.e., 10,000 or 12,000 lipase unit capsules/tabs taken 3-4 times over the course of the meal)
Other Causes of EPI	Alternative or concomitant diagnosis or cause (including small intestinal bacterial overgrowth, cancer treatment side effects, clostridium difficile infection, lactose intolerance, celiac disease or other malabsorptive causes)	• Rule out other diagnosis or cause • Address these causes as able

be a challenge due to MCT oil's limited palatability. It is important to note that while coconut oil is a natural source of MCTs, it also contains long chain triglycerides (LCTs) and therefore should not be used in place of conventional MCT oil.

EPI Management in Enteral Nutrition

EPI management for a patient receiving enteral nutrition poses a unique challenge. A simple first step is to utilize a low-fat, semi-elemental enteral formula to provide fewer LCTs and more MCTs to decrease dependence on pancreatic lipase for absorption. In some patients, this may be adequate to avoid symptoms of EPI. If EPI symptoms persist despite the use of a semi-elemental formula, an elemental formula may be beneficial (see malabsorption guideline free on-line at: https://www.guidelinecentral.com/guideline/502778/pocket-guide/502784/). Variable tolerance and difficulty meeting nutrition needs with lower calorie per mL formula/s are limitations of using an elemental formula for EPI management.

Administration of PERT to aid in the digestion of enteral nutrition can be cumbersome and difficult to administer properly to fully address EPI (especially those who infuse during the night while they sleep). An in-line digestive enzyme cartridge (Relizorb®, Alcresta, U.S. – https://www.relizorb.com/) provides a less burdensome option. The cartridge contains covalently bound and immobilized lipase that hydrolyzes fats to triglyceride form as the formula flows through it before ingestion. However, use is limited to pump feedings and some enteral formulas have more efficacy than others (https://www.relizorb.com/pdf/Compatible-Formulas-and-Pumps.pdf). The in-line digestive cartridge has been shown to provide >90% fat hydrolysis of polymeric and semi-elemental formulas and enhance lipid absorption from selected enteral products.[18]

In patients with EPI and gastric outlet obstructions, external biliary drains or drains due to enterocutaneous fistula of the upper GI tract or upper GI anastomotic leak, it may be beneficial to reinfuse bile and pancreatic enzymes alongside *jejunal* enteral nutrition.[19,20] Appropriate patient selection is critical as well as a consideration of nursing time involved in the era of staffing shortages.[20]

Evaluating Adequacy of EPI Treatment

There are several factors to monitor to determine the adequacy of EPI treatment. Gastrointestinal symptoms (as outlined in table 2) that were present before EPI treatment should show improvement with adequate intervention if symptoms are being driven by EPI. In patients with complex medical conditions or treatments, it can be difficult to determine symptoms and the multiple contributors should be considered when evaluating the adequacy and impact of EPI treatment.

Adequate EPI treatment should result in improved energy level, weight, and strength. Weight and strength gains are often gradual, more subtle improvements as compared to gastrointestinal symptoms and energy level. Adequate EPI treatment should result in the normalization and maintenance of fat-soluble vitamin levels (A, D, E and K), after appropriate repletion. Additionally, with improved absorption and fat-soluble vitamin levels, dual energy x-ray absorptiometry (DEXA) scan results should stabilize or improve. Routine monitoring of fat-soluble vitamin levels and bone density should be performed in patients with suspected EPI, starting at presentation. Thorough assessment and documentation of gastrointestinal symptoms and nutritional status are necessary at baseline and throughout care to assist in evaluating the efficacy and adequacy of EPI treatment. Although beyond the scope of this article, PERT treatment can uncover what might have been subclinical diabetes (Type 3c) in those suffering from undiagnosed EPI and malabsorption, once they finally begin to absorb their food.[29]

CONCLUSION

EPI prevalence is associated with numerous causes and, if left untreated, has negative impacts on nutrition status, may precipitate comorbidities, and significantly alter quality of life. Early identification and adequate intervention are necessary. Understanding the available interventions and appreciating the nuances of EPI treatment will promote improved care to patients suffering from EPI. See Table 6 for reasons why EPI may not achieve success. ■

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Answers to this month's crossword puzzle:

1 D	I	2 V	E	3 R	T	4 I	C	5 U	L	6 I	T	7 I	S	
I		O		E		M		N		N		N		
8 G	A	M	M	A		9 P	R	O	C	T	I	T	I	10 S
E		I		11 D	U	E				E		A		U
12 S	I	T	E			13 D	R	A	I	N		14 K	I	T
T		S		15 G		E				S		E		U
16 I	N		17 B	A	N	D		18 G	A	I	N		19 D	R
O		20 B		L				R		V		21 E		E
22 N	23 I	L		24 L	A	25 C	T	O	S	E		26 S	O	S
	27 C	O	28 O	S		A		I		C		C		
29 H	E	A	R	T	B	U	R	N		30 A	C	U	T	31 E
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32 A	N	I	O	N		33 T	A	34 S	T	E		35 E	Y	E
R		N		E		I		E				N		M
36 T	A	G		37 S	E	C	R	E	T	E		38 T	E	A