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## Pancreatic Enzyme Replacement Therapy: A Concise Review

Gregory T Brennan<sup>1</sup>, Muhammad Wasif Saif<sup>2</sup>

<sup>1</sup>Division of Gastroenterology, University of California Irvine, Orange, California

<sup>2</sup>Deputy Physician-in-Chief and Director, Medical Oncology at Northwell health Cancer Institute Professor, Medical Oncology, Zucker School of Medicine, Hempstead, New York

### Abstract

Pancreatic enzyme replacement therapy is safe and effective at treating pancreatic exocrine insufficiency. There are multiple causes of pancreatic exocrine insufficiency including chronic pancreatitis, cystic fibrosis and pancreatic cancer. Testing fecal elastase-1 level is useful for the diagnosis of pancreatic exocrine insufficiency. Starting doses of pancreatic enzyme replacement therapy should be at least 30–40,000 IU with each meal and 15–20,000 IU with snacks. pancreatic enzyme replacement therapy should be taken in divided doses throughout meals. Patients who do not respond to initial dosages should be evaluated for alternative etiologies and pancreatic enzyme replacement therapy optimized. Despite ease of use and benefit of pancreatic enzyme replacement therapy, challenges still remain clinically and this review hopes to provide a concise guide for clinicians.

### Keywords

Exocrine Pancreatic Insufficiency; Pancreatic Neoplasms; Pancreatitis; Chronic; Steatorrhea

### INTRODUCTION

Pancreatic exocrine insufficiency (PEI) is defined as inadequate activity or deficiency of the pancreatic enzymes within the intestinal lumen, resulting in maldigestion and malabsorption. The mainstay of treatment for PEI is pancreatic enzyme replacement therapy (PERT). PERT is a safe and effective therapy for PEI but supplementation is frequently forgotten or under-dosed [1] in patients because PEI can be difficult to diagnose.

Normally, the exocrine pancreas secretes digestive enzymes including lipase, elastase, amylase, trypsin and chymotrypsin into the second portion of the duodenum via the pancreatic duct. Stimulation of pancreas secretion is mediated by hormonal and neuronal control. When gastric contents (chyme) empty into the duodenum, secretin and cholecystokinin (CCK) are secreted. In response to acid, secretin stimulates pancreatic

**Correspondence** Muhammad Wasif Saif, Deputy Physician-in-Chief and Director, Medical Oncology at Northwell health Cancer Institute, Professor, Medical Oncology, Zucker School of Medicine, Northwell Health Cancer Institute 1111 Marcus Avenue, Suite: 216, Lake Success, NY 11042, **Tel** + 516-321-2238, **Fax** + 516-321-2272, [wsaif@northwell.edu](mailto:wsaif@northwell.edu).

Conflict of Interest

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release of bicarbonate and water. In response to fat and protein, CCK stimulates release of pancreatic enzymes [2]. Adequate mixing of chyme and these secretions is critical and can be disrupted by altered surgical anatomy or gastric acid.

### Causes of Pancreatic Exocrine Insufficiency

PEI is the consequence of several different diseases which all share a common pathophysiologic end result of inadequate enzyme digestion. Mechanisms of PEI include inadequate synthesis and secretion of pancreatic enzymes, decreased stimulation, pancreatic ductal obstruction and decreased pancreatic enzyme activity in the small bowel. Some of the common causes of PEI are chronic pancreatitis, pancreatic adenocarcinoma, and cystic fibrosis. A more extensive list is presented in Table 1. The differential diagnosis includes other causes of chronic diarrhea such as celiac disease, small intestinal bacterial overgrowth (SIBO), giardiasis, crohn's disease, microscopic colitis and irritable bowel syndrome. PEI should be considered in patients with risk factors for pancreatic disease or chronic unexplained diarrhea.

Chronic pancreatitis (CP) is an irreversible inflammatory process characterized by the destruction of the pancreatic parenchyma and ductal structures [3]. CP is the most common cause of PEI in adults [2]. Up to 85% of patients with advanced CP have PEI [4]. The diagnosis of CP is clear in patients with chronic abdominal pain with overt exocrine or endocrine dysfunction along with imaging demonstrating pancreatic atrophy, ductal changes or calcification [3]. Imaging can show diffuse pancreatic calcification. Computed tomography (CT) using pancreas protocol and magnetic resonance Imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) with or without secretin, are vital in the initial evaluation of suspected PEI. Cross sectional imaging should be obtained in adult patients with steatorrhea to rule out pancreatic cancer and evaluate for structural changes of the pancreas. Endoscopic ultrasound (EUS) provides detailed images of the pancreas and is appropriate in cases where the diagnosis is elusive or contraindications exist for MRI or CT. On EUS, parenchymal features in CP include hyperechoic foci, hyperechoic strands, lobularity, and cysts. Ductal features of CP on EUS include main duct dilation, duct irregularity, hyperechoic duct margins, visible side branches, and stones [3]. In CP, PERT reduces steatorrhea, enables normal dietary fat intake and allows for weight gain [5]. Randomized controlled trials have shown PERT improves steatorrhea, decreased stool frequency and fecal fat [1]. There is some evidence that non- enteric formulations (viokase) of PERT improves pain in CP1 but this is not conclusive base on the entire body of evidence. Non-enteric formulations must be given with acid suppression to prevent enzyme degradation. PERT is required indefinitely in CP once exocrine insufficiency begins.

Pancreatic cancer causes PEI when there is loss of pancreatic parenchyma and/or obstruction of the main pancreatic duct. Surgical resection or radiation for the treatment of pancreatic cancer also contributes to PEI. It is important for clinicians to recognize that PEI is near universal in patients with locally advanced or metastatic pancreatic cancer, with as high as 90–100% of patients affected [6]. Patients with weight loss, symptoms of malabsorption, or malnutrition should receive PERT. This is an important patient population needing PERT that is frequently forgotten. In one study, 50% of patients with symptoms of PEI were not

treated with PERT [7]. The benefit of PERT in patients with pancreatic cancer has been studied with conflicting results. PERT is believed to improve quality of life and maintains weight in patients with pancreatic cancer [1,8]. In a randomized controlled trial of patients with unresectable cancer in the head of the pancreas after biliary stenting, PERT prevented weight loss [8]. In a 2016, prospective, double-blind, randomized, placebo-controlled trial, PERT failed to show a reduction in weight loss or survival benefit in patients with unresectable pancreatic cancer [9]. Other studies however, have shown survival benefits of PERT in patients with unresectable disease [10]. In a 2018 retrospective analysis of patients with unresectable pancreatic cancer and PEI, PERT was associated with longer survival especially in patients with significant weight loss [10]. Despite conflicting data, PERT remains an important part of the supportive and palliative care of these patients because it improves quality of life [1,4].

Patients with cystic fibrosis have dysfunctional secretion of pancreatic enzymes as a result of mutations in the CF transmembrane conductance regulator (CFTR) gene.

Pancreatic insufficiency is the most common gastrointestinal complication of CF. It affects approximately 80% of CF patients [1]. In CF patients with steatorrhea, PERT should be started. Fibrosing colonopathy is a severe intestinal fibrotic process associated with very high doses of PERT in CF patients [11]. Therefore, care should be taken to avoid exceeding recommended doses (<10,000 lipase units per kg per day) [4].

### Approach to the Patient

Symptoms of PEI include mild abdominal discomfort, bloating, cramping, and increased flatulence. Patients with severe insufficiency have steatorrhea (loose, greasy, foul-smelling, voluminous stools that are difficult to flush, float or stick to the bowl) and weight loss. Steatorrhea and weight loss develop late in the disease process after there is loss of 90% of pancreatic secretion [2]. Therefore, PERT aims to supplement at least 10% of estimated pancreatic lipase to correct steatorrhea and improve digestion<sup>4</sup>.

The diagnosis of PEI is best made by a combination of history, ruling out other causes of malabsorption, cross sectional imaging of the pancreas and diagnostic tests. The most practical approach involves testing that is noninvasive, inexpensive and readily available. Such available labs tests are “indirect” measures of pancreatic function including fecal elastase-1, fecal fat measurement, and fat soluble vitamin measurements. A fecal elastase-1 level less than 200 µg/g is abnormal and commonly used as a cutoff point for the diagnosis of pancreatic exocrine insufficiency. The sensitivity of fecal elastase-1 increases (up to 100%) as the degree of PEI becomes more severe [2]. Levels <100 µg/g indicate severe PEI. Fecal elastase-1 measurements are not affected by PERT but can be falsely low in the setting of watery diarrhea from dilution. Patients with severe exocrine pancreatic insufficiency have elevated levels of fecal fat. Steatorrhea is defined as greater than 7 grams of fat per 100 grams of stool per day. Samples with greater than 14 grams of fat per 100 grams of stool per day is indicative of severe fat malabsorption. The gold standard for diagnosis of steatorrhea is a 72 hour quantitative measurement of stool fat but is cumbersome and rarely used. A spot stool sample for qualitative testing can be performed but is more prone to erroneous results based on fat intake and other diarrheal diseases may cause false positives. Patients with long

standing steatorrhea are at risk for deficiencies of the fat soluble vitamins: A, D, E, and K. Cross sectional imaging is indicated in adult patients with new onset steatorrhea and/or weight loss in order to obtain a structural evaluation of the pancreas<sup>4</sup>. A C-mixed triglyceride breath test less than 29% can diagnosis PEI however, this protocol is not routinely used in the U.S. [12,13].

### **Pancreatic Enzyme Replacement Therapy**

Formulations available in the United States are enteric coated (Creon, Zenpep, Pancreaze, Pertzze) and non-enteric coated (Viokase) [2]. Enteric coating prevents the enzymes from being denatured by gastric acid and the coating dissolves in the duodenum [1]. All available formulations are derived from porcine origin [2]. Finding the ideal dosing of PERT for a particular patient can be challenging because the response to treatment is widely variable from patient to patient. In general, enteric coated formulations are preferred because of gastric acid protection. In addition, microsphere formulations have a theoretical advantage of increased mixing over tablets [12]). In practice, the choice of formulation will also be determined by cost and insurance coverage of the individual patient.

Multiple studies have estimated that at least 30,000IU (or about 90,000 USP units) of lipase delivered to the intestine with each meal should eliminate steatorrhea [1,2,13]. This amount represents approximately 10% of normal pancreatic secretion<sup>4</sup>. The goal is not to replace 100% of estimated pancreatic function since steatorrhea only develops in severe disease. Therefore, starting doses should be between 30–40,000 IU with every meal and 15–20,000 IU with snacks [1,2,4]. Patients should be instructed to take ½ the total dose with the first bite of the meal and other ½ either during the meal or at the end of the meal.

When high doses are needed, prescribing higher strength capsules will reduce pill burden and improve compliance [1].

Several factors determine the response to treatment including degree of residual pancreatic function, anatomy, and the size and fat content of meals [1,4]. Because of differences in remaining pancreatic secretion and gastric production of lipase therapy must be tailored to the individual patient, based on severity of symptoms and response to treatment [2]. The response to PERT should be gauged by improvement in symptoms including stool consistency, loss of visible fat or oily droplets in the stool and weight gain [2]. Repeating fecal fat measurement can help gauge response (as can breath testing if available). Of note, fecal elastase-1 measures will not be affected by PERT and should not be used to guide dose adjustments. Fat soluble vitamins should be periodically checked to ensure adequate supplementation.

Patients who fail to improve with PERT should be carefully reassessed for compliance to treatment and correct timing of doses in relation to meals. Ruling out alternative causes for steatorrhea when patients fail to respond to PERT is important (Tables 1 and 2).

The most common reason for failure is inadequate dosage. Either the patient requires more enzyme or the timing of delivery is off, resulting in inadequate mixing of enzymes with chyme in the duodenum. In patients taking the PERT correctly, the first step would be to

double the dose of enzyme. The addition of acid suppression with proton pump inhibitors (PPI) or histamine 2 blockers (H2B) is a reasonable next step in patients with suboptimal response. On occasion, changing formulations may improve symptoms if dosage increases and acid suppression fails to improve symptoms.

A dietary history should be reviewed to determine fatty food intake. Restricting dietary fat may result in improvement of symptoms but a careful balance between adequate necessary intake of fat and fat soluble vitamins is important. Therefore, in the setting of PERT patients should not restrict dietary fat intake.

In addition to PERT, lifestyle changes are paramount in the management of patients with PEI. All patients should be counseled to stop smoking and drinking alcohol. Smoking and alcohol are involved in the pathogenesis of the chronic pancreatitis [2]. Smoking and alcohol use are both risk factors for pancreatic adenocarcinoma. In patients with chronic pancreatitis, alcohol cessation may slow progression of the disease. Alcohol can decrease lipase activity and make successful PERT difficult to achieve. A summary of the approach to PERT management is provided in Table 2.

## CONCLUSION

Pancreatic enzyme replacement therapy is safe and effective at treating pancreatic exocrine insufficiency. Chronic pancreatitis and pancreatic cancer are the most common causes of pancreatic exocrine insufficiency in adults and clinicians should have a high index of suspicion in these patients. PERT is under-utilized in the management of pancreatic cancer and has been shown to improve quality of life and may improve survival in these patients. In patients with these risk factors and suggestive symptoms, we recommend starting PERT given its safety and efficacy. A fecal elastase-1 level < 200 µg/g is abnormal and useful for the diagnosis of pancreatic exocrine insufficiency.

Testing for abnormalities in fecal fat and fecal elastase-1 are especially helpful in some patients with minimal or no symptoms. We recommend starting doses of PERT should be at least 30–40,000 IU with each meal and 15–20,000 IU with each snack. Patients should be instructed to take ½ the total dose with the first bite of the meal and the other ½ during or immediately after the meal. Patients who do not respond should be evaluated for other etiologies such as small bowel bacterial overgrowth. Strategies to optimize PERT should begin with doubling the dose.

## Abbreviations

<b>PERT</b>	pancreatic enzyme replacement therapy
<b>PEI</b>	pancreatic exocrine insufficiency

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**Table 1.**

Causes of pancreatic exocrine insufficiency and mechanisms.

Cause	Mechanism
Chronic pancreatitis	Permanent structural damage of ducts and parenchyma
Cystic fibrosis	Dysfunctional pancreatic secretion secondary to CFTR mutations
Main pancreatic duct obstruction	Decreased secretion of pancreatic enzymes
Pancreatic resection	Decreased secretion of pancreatic enzymes
Gastric resection	Decreased hormonal stimulation, rapid transit, inadequate mixing of chyme with pancreatic enzymes
Short bowel syndrome	Decreased hormonal stimulation, rapid transit, inadequate mixing of chyme with pancreatic enzymes
Hereditary hemochromatosis	Iron deposition in the pancreas
Celiac disease	Small bowel mucosal disease leads to decreased CCK mediated pancreatic stimulation
Zollinger-Ellison syndrome	Gastrinoma causes inactivation of pancreatic enzymes via increased gastric acid

**Table 2.**

Pert management summary.

<b>PERT MANAGEMENT SUMMARY</b>	
1. <i>Lifestyle modification</i>	Complete cessation of smoking and alcohol consumption.
2. <i>Diet</i>	Recommend a healthy diet; dietary fat restriction is not required. Smaller more frequent meals may improve symptoms.
3. <i>Start with an adequate dose of PERT</i>	30–40,000 IU with each meal and 15–20,000 IU with snacks.
4. <i>Timing is important</i>	PERT should be taken with both meals and snacks; if several capsules are required, they should be taken at various times before, during and after eating.
5. <i>Ensure follow up &amp; assess response</i>	Monitoring response to treatment is important. Careful evaluation for other causes in patients not improving; including pancreatic cancer (EUS, imaging), celiac disease (TTG IgA), giardia (stool antigen), SIBO (breath test), irritable bowel syndrome, and mucosal disease (endoscopy).
6. <i>Step-wise optimization of PERT</i>	<ul style="list-style-type: none"> <li>a. Assess compliance &amp; reinforce importance of daily dosing with all meals and snacks</li> <li>b. Increase the dose of PERT (double the dose)</li> <li>c. Trial of concomitant PPI or H2B therapy</li> <li>d. Switch formulation</li> </ul>