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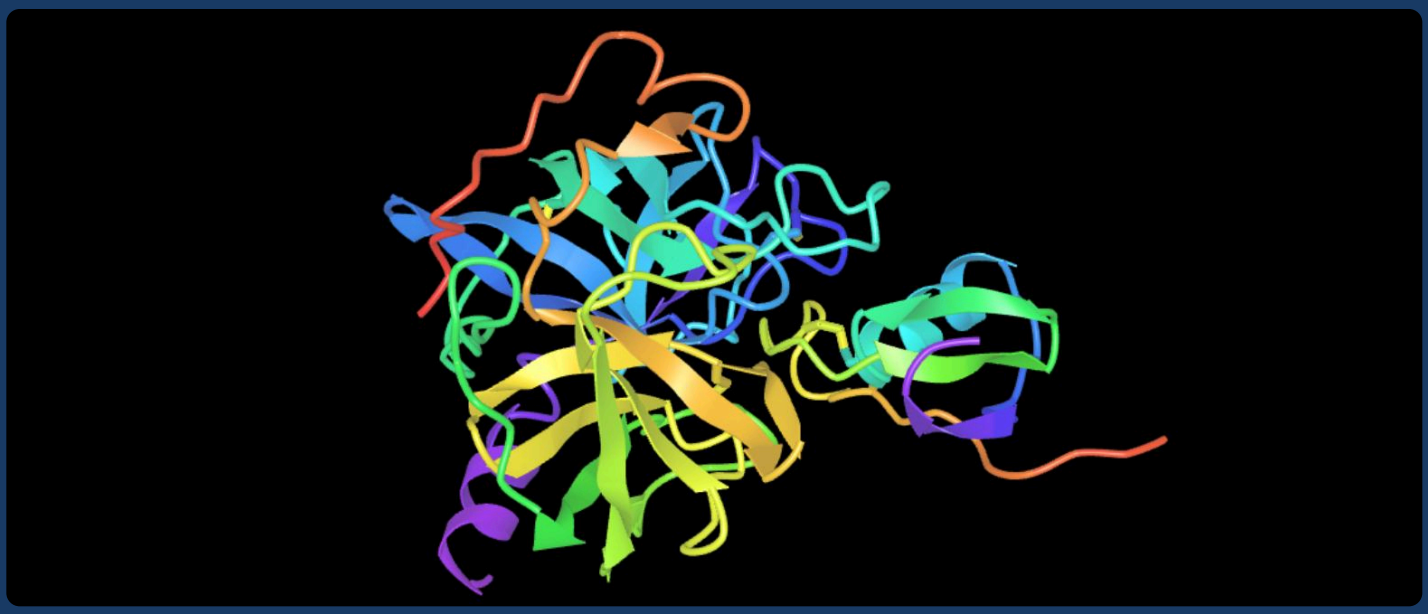

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Maham Waqar MD,
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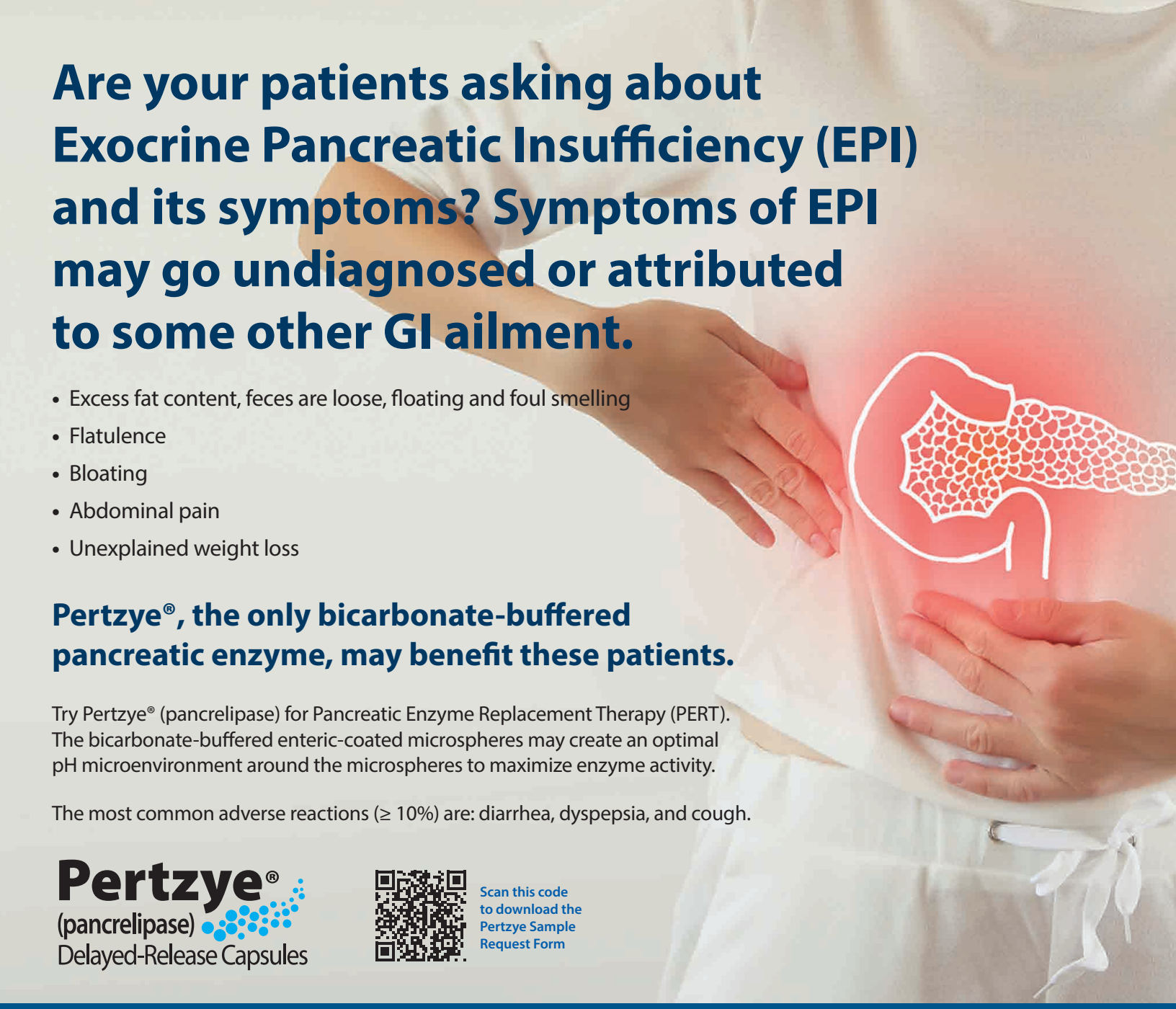

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SMART Medical Review

Pancreatic Enzyme Replacement Therapy: Background, Indications, and Pitfalls

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Abstract: This review outlines the history, physiology, clinical circumstances, pharmacology, pitfalls and proper implementation of exogenous pancreatic enzyme replacement therapy (PERT).
Humanity has used PERT for hundreds of years—but in the last 30-50 years with much improved precision. Some topics that will be reviewed here include the complex diagnosis, prevalence, and long-term complications of Exocrine Pancreatic Insufficiency (EPI) and resultant dysfunction in Digestive Capacity (DC). The indications, efficacy, and safety of PERT in EPI will be discussed. Optimizing PERT is not as easy as it seems. Many practical tips for PERT optimization are outlined for the reader.

Key words: Digestive Capacity, Exocrine Insufficiency, steatorrhea, pancreatic enzyme replacement, PERT, PEP, chronic pancreatitis, malabsorption, maldigestion, bloating, flatulence, diarrhea, SIBO, Bacterial Overgrowth, Failure to Thrive, Wasting, Pancreatic atrophy, Fatty pancreas, Pancreatic Cancer, Pancreatic surgery, Practical, Clinical, History of PERT or PEP

Outline:

1. Background

Pancreatic Enzyme Products as Digestive Aids

Pancreatic Enzyme Products/Preparations (PEP) aim to package the most important pancreatic secretory enzymes into a form that can be ingested or otherwise used to facilitate digestion. PEPs were first used in the 1800's as digestive aids. In the 1850s, investigators found that the exocrine pancreas facilitated fat absorption, and by the 1890s,

Abbreviations used in this paper: PEP, pancreatic enzyme products; DC, digestive capacity; PERT, pancreatic enzyme replacement therapy; FE-1, fecal elastase; EPI, Exocrine Pancreatic Insufficiency; SIBO, small intestine bacterial overgrowth; H2, histamine receptor 2; MCTs, medium chain triglycerides.

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others had found that the pancreas had a similar role in protein absorption.[1] It was first appreciated that passage through the stomach interfered with the actions of unprotected exogenous pancreatic enzymes in 1879.[2] The 1910s-1940s witnessed the first attempts at adding enteric coatings to try to protect the exogenous pancreatic enzymes from gastric passage, with variable results. In the 1980s, technology permitted filling a standard size capsule pill with multiple microspheres, microbeads, microtablets or microcapsules of acid-resistant enzymes, and, thereby, the modern era of pancreatic enzyme replacement began.[3] For a variety of reasons, including concerns regarding shelf life and overfilling, the FDA decided in 2004 to regulate these products as drugs and required that all manufacturers provide safety and efficacy data for their pancreatic enzyme replacement products.[4] But even after 100s of years of study, many questions remain.

2. Questions on use of PEP as Pancreatic Enzyme Replacement Therapy (PERT)

- When should pancreatic enzymes be prescribed?
- Who is most likely to benefit from PERT?
- Which PEP should be chosen and at what dose?
- How can patient's outcomes be optimized?
- What are some of the consequences of PERT?

Physiology of Pancreatic Digestive Enzymes

Before discussing proper implementation of pancreatic enzyme replacement therapy, a review of endogenous pancreatic enzyme production and pancreatic digestion is needed. Much of the terminology in this field is confusing, and it is worthwhile to walk through digestion, exocrine function/physiology and its associated vocabulary.

Digestion is a complex process and mild to moderate dysfunction in a single area of the gastrointestinal tract (or in single step in digestion) can lead to poor nutrient absorption. This poor nutrient absorption represents "dysfunction" in the digestive capacity (DC) of the GI tract. DC can be measured in a number of ways, such as with fecal fat analyses, the D xylose malabsorption test, stool levels of alpha1 antitrypsin, and the Schillings test to name just a few. In this article, we will focus on disruptions in the DC (see table 1) that can respond to treatment with exogenous PEP.[5] Table 2 lists a number of PEP's that are available in the USA.[3]

The pancreas plays a critical role in maintaining sufficient DC and promoting nutrient absorption. For example, the pancreas produces the vast majority of the digestive enzymes and optimizes the milieu required for adequate digestion. The pancreas has significant excess production capacity, and insufficient endogenous digestive enzyme production is generally not seen until 90% or more of the pancreas has become dysfunctional.[6] This ability of the pancreas to contribute to digestive capacity is termed pancreas exocrine function.

Table 1: Causes of impaired digestive capacity and prevalence of exocrine insufficiency.[5]

CONDITION	PREVALENCE OF EPI (%)
Chronic Pancreatitis	30-90
Acute Pancreatitis	15-40
Autoimmune Pancreatitis	30-60
Unresectable Pancreatic Cancer	20-60
Pancreaticoduodenectomy	80-90
Distal Pancreatectomy	20-50
Cystic Fibrosis	80-90
Type I Diabetes*	30-50 meta-analysis[43]
Type II Diabetes*	20-30 meta-analysis[43]
Inflammatory Bowel Disease	5-10
Intestinal Transplantation	10
HIV/HAART Therapy	10-50
Gastrectomy	40-80
Esophagectomy	16
Aging, esp over 80	15-30
Tobacco Smoking	10-30
Octreotide	20
Celiac Sprue	5-80
Roux-en-Y	9-43 by inference/plausibility[41]
SIBO (Bacterial Overgrowth)	5-40 by inference/plausibility[42]

Table 2: Pancreatic Enzyme Preparations in USA[3]

Trademarked Preparation	Doses available (USP Units)*	Delivery (size mm) varies by dose
Creon	6,000, 12,000, 24,000, 36,000	Minimicrospheres (0.7-1.6)
Pancreaze	4,200, 10,500, 16,800, 21,000, 37,000	Microtablets (2)
Pertzye	4,000, 8,000, 16,000, 24,000	Bicarbonate buffered Microspheres (1.8-2.2)
Relizorb	1 cartridge per 500ml feed	N/a (for external use only)
Ultresa	13,800, 20,700, 23,000	Minitablets (2)
Viokace	10,440, 20,880	N/a (uncoated)
Zenpep	5,000, 15,000, 25,000, 40,000	Enteric coated beads (1.8-2.5)

*Other Strengths are often available as well. Just a sampling is shown.

Other organs, such as the salivary gland, stomach, liver, bile ducts and small intestine, assist the exocrine pancreas in producing digestive enzymes and/or in providing for the proper microenvironment for digestion contributing to DC.

As the pancreas becomes more and more dysfunctional, higher levels of pancreas exocrine dysfunction can be observed, leading to a progressive reduction in DC. It is generally accepted that pancreas exocrine dysfunction (and resultant dysfunction in DC) begins when more than 7% of the fat/lipid ingested is secreted into the stool and when the concentration of a pancreatic enzyme called fecal elastase (FE-1) in stool is less than 200mcg/gm feces (when the correct testing conditions and appropriate clinical context have been met). A previous issue in this journal addressed the proper use and interpretation of the FE-1 test, keeping in mind, nonpancreatic conditions can cause abnormal fecal fat and fecal elastase tests.[7] More precise tests of pancreatic exocrine function such as the secretin stimulation test[8], the secretin-cholecystokinin stimulation test, the secretin-MRI test, the mixed triglyceride breath test[9], the bentiromide test, and the serum trypsin level are generally not available to most clinicians. A detailed discussion of tests/interpretation/diagnosis for Exocrine Pancreatic Insufficiency (EPI) is beyond the scope of this article.[10] However, a recent summary on exocrine pancreas dysfunction[11] modified older conceptual framework[12] and suggested dividing pancreas exocrine dysfunction into 4 stages, eventually leading to EPI, typically at 15% or less absorption of dietary fat and at FE-1 levels of less than 100mcg/gm, usually less than 50mcg/gm. Determining levels of certain nutrients, especially vitamins A, D, E, K, B12, and magnesium can help stage patients' exocrine pancreas dysfunction using the above staging system. For additional reading on this topic, I suggest an excellent recent review that outlines many of the challenges in EPI.[13]

Why is EPI a problem?

EPI is a significant clinical problem for multiple reasons. Although the prevalence of EPI is not precisely known, it is fairly common. Table 1 includes estimates of the prevalence if EPI in certain populations.[5] Furthermore, EPI results in a number of adverse clinical outcomes such as atherosclerosis/cardiovascular disease, increased bone fractures[14], decreased survival, especially in cancer patients[15], reduced healing/resolution of functional capacity after surgery, altered microbiome[16], and so forth. EPI can be the "canary in the coal mine" for the clinician, indicating that a precancerous main duct IPMN (Intraductal Papillary Mucinous Neoplasm) or a PANIN3 (Pancreatic Intraductal In Situ Neoplasm) is present. It is also well described that clinicians underrecognize and undertreat EPI and its consequences.[17,18]

Numerous conditions, diseases, and medications contribute to EPI and result in reduced DC. Chronic pancreatitis would be the prototypical disease, but other disease states are important contributors to EPI, such as surgical resections/manipulations[19], small bowel bacterial overgrowth, acute pancreatitis, pancreatic cysts, diabetes, gastroparesis, ileus, rapid transit time, HIV, etc. (table 1). Medications and supplements can also contribute (orlistat, olestra™/olein™, ezetimibe, octreotide, etc) to EPI.

Whom should be treated with PERT?

It has been suggested that PERT should be used when EPI is present. In fact, several randomized controlled trials have demonstrated the efficacy of PERT in the presence of EPI.[20,21,22] Uncoated PERT with acid suppression is also effective at ameliorating EPI.[23,24] In some cases, PERT can be used in patients with certain other disruptions in DC, albeit without an FDA approved indication.

However, a trial of PERT is reasonable in the correct clinical context at earlier stages of exocrine pancreatic dysfunction, if such dysfunction is a significant detriment to patient quality of life or could pose significant challenges to future medical procedures and interventions. It is important to note that clinical signs and symptoms, such as steatorrhea, are insensitive and also have a modest false positive rate as well. Marked pancreatic steatorrhea can be

present with one single hard bowel movement per day. Steatorrhea due to pathology of the small intestine is often bulkier and more voluminous, but, again, this is not a definitive symptom or sign. Furthermore, many GI patients complain of gas, foul stool, and excreting "undigested" material and these alone, without supportive testing, also are not definitive for the presence of EPI. Thus, it is incumbent upon the clinician to remain vigilant for the clinical clues that might suggest early exocrine dysfunction and yet avoid overdiagnosis. Some clinical clues that a patient may be suffering from EPI include failure to thrive, small height, weight and physical strength for family and age, foul gas, foul stools, frequent/loose stools, oily/greasy hard to wipe floating stools, ring around the toilet bowl, high caloric intake in spite of small size, sarcopenia, reduced strength and endurance, passage of undigested material in stool, hypomagnesemia, low zinc, osteoporosis/osteopenia, poor wound healing, recurrent calcium oxalate renal stones, slightly elevated INR, slightly low albumin, incidental pancreatic atrophy/incidental pancreatic steatosis on imaging, etc.

In the past, pancreatic enzymes had been promoted to help with pancreatic pain or even to reduce the frequency of acute pancreatitis attacks.[25,26] In doing so, it is crucial to separate pancreatic pain from malabsorptive pain, the latter of which definitely can improve on PERT.[27] More recent guidelines advise against a trial of PERT for pain in chronic pancreatitis.[28] However, given the excellent side effect profile, a short trial of PERT for pancreatic pain is reasonable.

PERT can also be used for nonpancreatic indications. There are theoretical reasons why this might be reasonable. For example, small intestinal bacterial overgrowth (SIBO) often coexists with EPI.[29] In fact, one mechanism for the development of small intestinal bacterial overgrowth (SIBO) is insufficient pancreatic enzyme production. Some have advocated for using PERT in patients suffering from SIBO, bloating, weight loss, and other digestive complaints. Many diabetics suffer from vagal neuropathy and a variety of other digestive problems. In fact, some investigators have found pancreatic insufficiency commonly in the diabetic population.[30,31] Whether this represents true, intrinsic pancreatic insufficiency (so called pancreatopathy of diabetes) or just false positive testing for EPI due to the diabetes/diabetic diarrhea in certain patients is a matter of some debate. The reader should be advised that although these are reasonable practices due to the excellent safety profile of PERT, these are not FDA approved indications for PERT.

What dose and type of PERT should be used?

In the USA, pancreatic enzyme products are dosed in USP units. For reference, one international unit (IU) = 3 USP (US pharmacopeia) units. Generally, patients should start with at least 40,000 USP lipase units with meals but most patients need a good bit more than that, typically in the range of 70-120,000 USP lipase units/meal and 20-60,000 USP lipase units with snacks.[32,33] Several pancreatic enzyme preparations are available to prescribers and patients (table 2). Recently, a novel product has been marketed to "pre-digest" enteral feeding formulations using a cartridge of active pancreatic lipase prior to infusion into the digestive tract of patients and to facilitate digestion.[34]

In the pediatric population, a typical recommendation would be 4000 units of lipase per gram of fat intake or 10,000 units of lipase per kg body weight per day.[35]

PERT is well tolerated and has an excellent side effect profile. Concerns over the development of colon strictures and damage (fibrosing colonopathy) from high dose pancreatic enzyme replacement remain unfounded outside of the pediatric population on excessively high doses of PERT. Gout flare is a very uncommon complication. Conversely, most patients on PERT are underdosed.[17]

What is the clinician to do when the patient is not responding appropriately?

Complete amelioration of EPI is not common during PEP therapy for a number of reasons, including economics, adherence, clinician vigilance, hyperacidity, altered anatomy, coexistence of multiple disorders (such as SIBO, fast transit time) and even intolerance. Many of these clinical suggestions are listed in Table 3.

When the clinician is faced with a patient who has ongoing EPI/reduction in Digestive Capacity, in spite of pancreatic enzyme replacement, several important questions should be asked.

Is the patient taking the enzymes? Many patients self-underdose to conserve their supply of enzymes, which can be expensive.

Is the patient taking them properly? For example, some of my EPI patients misunderstand and take the enzymes every 8 hours regardless of PO intake.

Is the dose sufficient? Does the dose match the food being consumed? Heavier, higher fat meals will require higher doses of PERT.

Is the duodenal pH too low/too acidic? Lipase does require an alkaline milieu for optimal activity.

Are there insufficient concentrations of bile salts to facilitate absorption? Bile salts disrupt fat droplets into smaller micelles to facilitate the action of lipases.

Is there another issue/disease contributing to symptoms such as SIBO, celiac disease, microscopic colitis, inflammatory bowel disease, alpha-gal syndrome, Common Variable Immunodeficiency, Giardiasis, Zollinger-Ellison syndrome, Protein losing enteropathy, NSAID enteropathy (or other medication side effect), carcinoid syndrome, amyloidosis, jejunal lymphoma, etc?

Table 3: Reasons for Failure of PERT

Reason for Treatment Failure	Solutions
Poor adherence	Financial Assistance; More counseling/teaching
Side effects (hyperglyc,constip)	Treat the side effects and adjust insulin, etc
Excess Acid	Add PPI and/or sodium bicarb or direct agent
Altered Anatomy	Change to (or add) uncoated enzymes
High Calorie/High Lipid diet	Increase Dose
Gastroparesis/Gastroduodenal Dyssynchrony	Divide the enzyme pills throughout the meal. \Consider prokinetic, Small frequent meals
SIBO	Treat the small intestinal bacterial overgrowth
Dysphagia	Open the capsules and take with soft food and wash down
Gastrostomy	Use the smallest minibeads or use lipase cartridges or gently crush uncoated enzymes
Poor micronutrient absorption	Take a Multivitamin twice a day with enzymes and food. Add MCT oils

Sometimes patients stop their PERT due to side effects such as constipation, which should be corrected. Occasionally, PERT can cause hypoglycemia from hyperinsulinemia or more commonly just hyperglycemia from increased nutrient absorption, etc, causing the patient to hesitate at taking the proper dose.

Currently, all PEP are derived from porcine sources and thus can be subject to supply chain disruptions and rare allergic issues or rare personal convictions.

Is gastroparesis or partial duodenal obstruction (which often occur in patients with EPI) causing dyssynchrony between enzyme and food delivery to the small intestine? Sometimes a prokinetic can be beneficial in gastroparesis patients.

Once the clinician has assessed for the above, a series of changes can be made.

Often taking the enzymes throughout the meal rather than just upon starting the meal can result in better mixing.[36]

Commonly, a different brand/formulation of enzyme will help patients with intractable EPI. Matching the right PEP formulation to the right patient is important. The dissolution of the various types of coated pancreatic enzymes on the market in ileal juice may vary between commercially available preparations.[3] This may account for some variability in the efficacy of these drugs during practical use. For example, switching from minispheres to microspheres and back to microtablets, and vice-versa sometimes is anecdotally beneficial in incomplete responders.

Should the patient change to an uncoated preparation (i.e. is there insufficient time for the coating to dissolve and mix properly with food)? This is a common issue in patients with altered anatomy such as from Roux en Y gastric bypass surgery or from pancreaticoduodenectomy or in those with rapid GI tract transit time. If a non-enteric coated enzyme is used, it should probably be prescribed with an H2 (histamine receptor 2) blocker or proton pump inhibitor to reduce acid-induced destruction of lipase. Some have argued that only high dose proton pump inhibitors (up to 60mg omeprazole equivalents divided into twice daily dosing) plus sodium bicarbonate at 1.3g (12mEq) at the beginning of a meal and perhaps at 1 hour and 3 hours after meals are necessary to achieve optimal lipase activity using uncoated preparations.[37] But keep in mind, it is known that using a proton pump inhibitor with uncoated preparations is quite effective at alleviating steatorrhea.[24] Some have suggested taking a modest dose of uncoated enzyme product at the start of the meal, when there is some rapid emptying of modest amounts of lipid, followed by a modest dose of coated enzyme during the meal, to help with the rest of the lipid in the meal.[3]

Adding an acid reducing therapy such as an H2 or PPI or vonoprazin (reversible potassium-competitive inhibitor of potassium/acid pump) is often helpful in many types of patients on PERT, even in those taking coated enzyme formulations. But anecdotally, reducing/eliminating the acid reduction therapy can sometimes also help. For example, proton pump inhibitors can cause diarrhea. Also, in some patients, especially in those who take coated pancreatic enzymes, acid reducing medications can cause the capsules and/or microspheres/minitablets to open too late, even in the ileum where there is often not sufficient time for absorption and inadequate mixing of the PEP with the chyme. Furthermore, it is important to avoid excessive calcium or magnesium intake at mealtime which can cause fatty acids to be poorly absorbed.[38]

EPI Patients with dysphagia or with feeding tubes can be challenging. Enteric coated formulations generally can be opened and taken by mouth with pureed food and can be flushed through feeding tubes carefully to avoid clogging.

Many pharmacists suggest using applesauce with the enzyme beads from the opened capsules. However, some have recommended against the use of applesauce or other acidic foods which might damage the enteric coating of the minibeads.[3] *Ex vivo* lipase cartridges are commercially available for tube feeding patients and are especially useful for those on continuous tube feeds.[32]

Sometimes it is useful to add medium chain triglycerides (MCTs) to the patient's regimen.[39] MCTs are present in small amounts in a normal balanced diet, but supplements can increase the proportion of fat in the diet from medium chain triglycerides substantially. MCTs do not require active pancreatic enzymes to be absorbed, unlike the typical long chain triglycerides prevalent in most diets. MCTs can also solubilize fat soluble vitamins and are commercially available at many grocery stores and via mail order. Unfortunately, MCTs have a low smoke point (cooking temperature at which an oil breaks down and begins smoking) and have a bit of an unpleasant odor. But in the dedicated patient, MCTs can play a role.

Multivitamins should be ingested with pancreatic enzyme supplements, a small meal or snack and some MCTs.

How do we monitor for clinical success with PERT?

Here, not much data is available. However, following vitamin and mineral levels in the blood every few years and obtaining DEXA bone density measurements every 3-5 years, as well as monitoring for other markers of nutrition, such as thigh circumference, grip strength, weight, albumin level and so forth seem reasonable. Recently, some investigators have become interested in monitoring for sarcopenia using the results of routine abdominal imagery obtained for other reasons.[40] Quantitative (72 hr.) fecal fat measurements are not done routinely. However, in rare circumstances, fecal fat measurements can be used to monitor for response. Remember that when comparing two different fecal fat measurements, the diet for the preceding 7 days or so for both tests, needs to be similar. There can also be day to day variability due to attacks of acute inflammation, recent gastroenteritis and other variables.[10] The fecal elastase test is not useful for this purpose since it does not detect nonhuman enzymes.

3. Conclusion

Humanity has used PERT for hundreds of years--but in the last 30-50 years with much improved precision. The efficacy and safety of PERT have been proven in EPI in multiple studies. The diagnosis of EPI is somewhat complex and beyond the scope of this paper, but many cohorts of patients suffer from EPI with a number of resultant long term health complications. Optimizing PERT is not as easy as it seems. Many practical tips for PERT optimization were outlined in this paper above. The future is bright for PERT and PEP: many hypotheses exist for further optimization of PERT and PEP.

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