Current Treatment Options in Gastroenterology (2025) 23:22
https://doi.org/10.1007/s11938-025-00486-4

REVIEW

Diagnosis and Management of Exocrine Pancreatic Insufficiency

Anam Bashir[1] · Asim Maqbool[1] · Virginia A. Stallings[1] · Jefferson N. Brownell[1]

Received: 24 March 2025 / Accepted: 11 November 2025 / Published online: 26 November 2025

Abstract

Purpose of Review Exocrine pancreatic insufficiency (EPI) may occur due to a variety of causes depending on the age of the patient, and making the diagnosis can be challenging due to a lack of reliable diagnostic testing approaches. This review summarizes the approach to diagnosis and treatment of patients with EPI.

Recent Findings In patients at risk of EPI, timely diagnosis and treatment are important to optimize nutritional status, quality of life, and survival. EPI without overt steatorrhea may be subclinical with nutritional impacts such as weight loss or growth failure and nutrient malabsorption. Providers should be familiar with available indirect and direct tests and know when such tests will facilitate accurate diagnosis and appropriate, prompt treatment.

Summary Identification of at-risk patients, appropriate diagnostic testing, and appropriate PERT dosing are necessary to provide quality care for patients with EPI.

Keywords Exocrine pancreatic insufficiency · Pancreatic enzymes · Steatorrhea

Introduction

Exocrine pancreatic insufficiency (EPI) is a general term that describes the consequence of inadequate concentrations of active pancreatic enzymes in the duodenal lumen following a meal. Effective diagnosis EPI requires a familiarity with the processes underlying normal digestion and absorption as well as the potential short- and long-term consequences of insufficient pancreatic enzyme activity. Successful treatment requires the recognition that digestion and absorption of all nutrients is impaired, and deficiencies must be considered and assessed beyond fat and fat-soluble vitamins. EPI is associated with increased mortality in patients with chronic diseases, including CP, CF, and pancreatic cancer [1–3].

EPI also contributes to reduced quality of life in patients with chronic conditions. A recent systematic review found that regardless of the underlying disease, EPI was independently associated with significantly lower quality of life (QOL) scores when comparing patients with the same disease [4].

Normal digestive pancreatic function depends on normal secretory activity of the two main types of cells in the exocrine pancreas: acinar cells and ductal cells. Acinar cells secrete the digestive enzymes, including amylases, lipases, and proteases, responsible for breaking down dietary macronutrients. Ductal cells secrete water and bicarbonate ions, the remaining two components in the pancreatic juices, responsible for conveying enzymes to the intestine and neutralizing gastric hydrochloric acid in the proximal duodenum. It is rare that either ductal or acinar components are independently impaired while the other is intact; however, some genetic disorders may negate only one component of this process. Furthermore, a number of etiologies external to the pancreas may cause functional EPI due to reduced activity of normally-secreted pancreatic enzymes (See Table 1).

The underlying etiology is likely to have a significant effect on a patient's presentation and treatment goals. The majority of evidence in the literature examines EPI in the context of one of a few major diseases: cystic fibrosis (CF), chronic pancreatitis (CP), and pancreatic cancer. Often, more general recommendations regarding diagnosis and treatment of EPI have been extrapolated from these populations.

✉ Jefferson N. Brownell
brownellj@chop.edu

[1] Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, USA

In reality, exocrine pancreatic function is a continuous rather than binary variable, and the clinician must be familiar with groups at high risk of developing EPI, appropriate diagnostic testing for EPI and how testing should be employed, and ultimately the comprehensive approach needed to manage a patient with EPI.

Diagnosing Exocrine Pancreatic Insufficiency

A persistent challenge to the accurate diagnosis and effective management of a patient with suspected EPI is the lack of an accurate and available diagnostic test. For tests that do exist, there remain inconsistencies in interpretation of results: for instance, a survey in 2022 of 329 European and African pancreatologists reported significant variability in the most appropriate cut-off value for the fecal elastase-1 test to discriminate between normal pancreatic function and EPI [40]. The lack of a widely-accepted, structured approach to testing requires the clinician to decide between less invasive and potentially less specific indirect tests of pancreatic function versus more invasive direct measurements of pancreatic function. In general, testing for EPI should be pursued if there is a relatively high clinical suspicion and pre-test probability.

Indirect Testing

Indirect tests are often the first line of assessment, primarily used to screen for EPI. These tests evaluate surrogate markers for pancreatic enzyme activity in stool, serum, urine or through breath tests, offering relatively noninvasive ways to assess EPI.

The most commonly-used indirect test is fecal elastase-1 (FE-1). FE-1 is produced solely by the pancreas, is not degraded in the intestine, and remains stable at room temperature, making its concentration in stool a viable indicator of pancreatic enzyme secretion [41]. The simplicity of the test makes it a frequent choice as it requires a random, small-volume stool sample. The commercially-available assay does not cross-react with porcine elastase, meaning that it can be performed while a patient is taking porcine-derived pancreatic enzyme replacement therapy (PERT). However, multiple challenges limit FE-1's utility as a diagnostic test. While FE-1 testing is effective in discriminating between severely impaired or normal exocrine function, it is unreliable in mild to moderate insufficiency. As noted above, there is significant disagreement among experts as to specific cut-off points. The specificity of the test increases with lower cut-off points: FE-1 concentrations < 100 µg/g of stool are widely considered abnormal, with some experts recommending a threshold of < 50 µg/g for greater diagnostic accuracy. It should be noted that lowering the cut-off increases specificity but sacrifices sensitivity. Another limitation to FE-1 testing is that it must be performed on formed stool. Watery stools dilute enzyme concentrations and can generate false negative results. Despite these challenges, FE-1 remains a useful method for assessing pancreatic function, especially when used in conjunction with clinical symptoms and other diagnostic tests [42].

The historical gold standard test for evaluating steatorrhea and thus exocrine pancreatic function is another indirect measure requiring stool collection, the coefficient of fat absorption (CFA). The CFA requires detailed dietary intake data as well as a 72-hour stool collection while consuming a higher-fat diet. The ratio of stool fat content is compared to total fat intake using the equation:

$$\text{CFA}\,(\%) = [(\text{grams of fat consumed} - \text{grams of fat in stool})\,/\text{grams of fat consumed}] \times 100$$

A normal CFA for infants is >85%, while normal for children and adults is >93%; however, some experts caution that results should be interpreted within the context of a patient's clinical symptoms, fat intake, and stool fat content [43].To reduce the burden of testing on the patient, 24-hour stool collections have been proposed and are considered by some to be adequate; however, this assumes a very routine dietary intake and defecation pattern [44]. However, the CFA is rarely used clinically due to practical limitations and its diagnostic utility. There is significant burden on patients to accurately record dietary intake information and collect stool for 72 h, and stools must then be shipped frozen to commercial reference laboratories [45]. Furthermore, CFA is not specific for EPI per se, as it simply detects dietary fat malabsorption. Other non-pancreatic etiologies may underly dietary fat malabsorption such as small intestinal bacterial overgrowth, Crohn disease, and liver disease [45].

Chymotrypsin testing in stool, another indirect measure, uses a photometric assay to assess enzyme activity. It is less reliable than FE-1, as it is prone to degradation during intestinal transit. Moreover, the presence of chymotrypsin in PERT complicates interpretation, requiring patients to stop their medication three days prior [45]. For these reasons, this test should not be used to diagnose EPI.

Three non-invasive and indirect tests evaluate pancreatic function by evaluating for a byproduct of a specific probe via pancreatic-based hydrolysis and are arguably more specific for EPI; however, they are not widely available:

The pancreolauryl test involves a dual substrate combining a lauric acid derivative, dilaurate, and fluorescein. When lipase hydrolyzes the substrate, fluorescein is released and may be detected in urine or blood. Addition of mannitol helps correct variations in intestinal permeability that may

Table 1 Etiologies of EPI

Genetic/Hereditary Causes	Inflammatory/destructive:	Cystic Fibrosis	Most common hereditary etiology of EPI. The majority of patients with CF have EPI (~80%); < 20% have exocrine pancreatic sufficiency, which can progress to EPI with successive bouts of pancreatitis. In the era of highly effective CFTR modulators, PI may be partially reversible with some recovery and improvement in residual function [5, 6].
	Hypoplasia	Shwachman-Diamond Syndrome	Clinical triad of EPI, hematological abnormalities and skeletal dysplasia. Most common pediatric etiology of hereditary bone marrow failure and the 2nd most common cause of hereditary EPI and associated with fatty replacement of acinar tissue; amylase may be the predominant enzyme affected and may have some residual exocrine pancreatic function and reserve. Can also have associated liver dysfunction, cardiac issues, intellectual disability and behavior issues [7, 8].
		Johanson-Blizzard Syndrome	EPI associated with atypical facial features including short stature, dental abnormalities, nasal abnormalities, endocrine axis abnormalities, sensorineural hearing loss, urogenital abnormalities, intellectual impairments [9].
		Monogenic Diabetes of Youth (MODY)	Monogenic diabetes; formally known as mature onset diabetes of the young. They are currently 14 known different types of MODY; type 8 is the most common associated with EPI [10, 11].
		Jeune Syndrome	Asphyxiating thoracic dystrophy. Associated with cystic kidney disease, hepatic insufficiency, cystic pancreatic masses, EPI and retinal abnormalities [12].
	Metabolic	Mitochondropathies: Pearson Syndrome	Pearson syndrome is associated with bone marrow failure, lactic acidosis and failure to thrive. EPI related to pancreatic fibrosis. Short life expectancy, usually within the first few years of life [13].
	Enzyme deficiencies		Isolated or selective pancreatic enzyme deficiencies are rare to infrequent. Isolated pancreatic amylase deficiency, colipase deficiency, and lipase deficiency have been described. Brush border enzyme deficiencies such as enterokinase deficiency have been described, but may also occur in the setting of inflammation and mucosal damage [14–19].
Acquired	Permanent		
	Endocrine/neuroendocrine	Diabetes	Known (bidirectional) relationship between the endocrine and exocrine pancreas. diabetic ketoacidosis associated with transient exocrine pancreatic insufficiency. Decrease endogenous stimulation [20–22].
		Gastrinoma	Zollinger-Ellison syndrome. Intraluminal deactivation of pancreatic enzymes [23].
		Congenital hyperinsulinism	May relate to medical suppression with somatostatin analogs and transient/associated EPI as opposed to related to surgical resections and loss of acinar mass [24–26].
	Transient		
	Infectious gastroenteritis		Usually is short term and transient [27].
	Malnutrition		Reversible with nutritional rehabilitation in young children [28].
Inflammatory, autoimmune	Pancreatitis (acute, recurrent or chronic)	Variety of causes, age specific, and by type.	Can be transient or longer term for acute and recurrent. Some genetic causes such as those related to PRS S1 mutations may predict recurrence risk for pancreatitis and rapid progression to EPI [29].

Table 1 (continued)

	Extra-pancreatic	Celiac disease, Crohn's disease; short-bowel syndrome; gastric bypass.	May be transient or longer term; with celiac disease, EPI has been diagnosed in ~26% of adults at the time of diagnosis, with normalization noted at the time that serology normalizes with strict adherence to a gluten-free diet. Hypothesis that with small bowel mucosal disease that there may be decreased cholecystokinin release, which results in diminished pancreatic secretions. With both Crohn's disease and short-bowel syndrome, there may be post-cibal/gastrointestinal asynchrony [30, 31]. With Crohn's disease, there may extra-intestinal pancreatic involvement; decreased endogenous stimulation is also possible independent of this [32, 33].
Surgical	Pancreatic resections	Pancreatic tumors such as SPN, ductal adenocarcinomas; IPMN	May in part depend on site and extent of resection, as well as age at which resections performed [34].
Age-dependent	Early infancy and childhood		Pancreas amylase expression is low and increases to adult levels by the 2nd to 3rd year of life. This deficiency is not thought to be of any clinical significance. Lipase levels are also low in the first few months of life and there may be some compensation for low lipase by pancreatic lipase -related protein-2 (a homologue of pancreatic lipase). Despite these deficiencies, steatorrhea is not pronounced in neonates as compared to older infants, suggesting compensatory mechanisms. Premature infants may have more marked deficiency in these pancreatic enzymes which recover with age [35–38].
	Age related decline in the elderly		EPI has been reported in the elderly and with aging [39].

skew the results, providing a more accurate measurement via a fluorescein/mannitol ratio [46]. However, when compared to FE-1, the pancreolauryl test is less accurate [45].

The carbon-13 (^{13}C) mixed triglyceride breath test uses a meal with fatty acids labeled with the stable carbon isotope, ^{13}C. The lipolytic byproducts in the presence of lipase are ^{13}C -labeled octanoate and monoacylglycerol, which are absorbed and eventually exhaled as CO_2, which is then measured for its $^{13}C/^{12}C$ ratio. The presence of ^{13}C indirectly reflects intestinal lipase activity [47]. The meal composition used for the test remains inconsistent, with recent studies showing comparable results using standardized nutritional drinks instead of the traditional toast and butter [48]. Although promising, this test is not available in the United States.

Finally, the malabsorption blood test (MBT) is a functional test that measures relative fatty acid absorption. The test compares the serum concentration of an administered free fatty acid (pentadecanoic acid, PA) to the serum concentration of a constituent free fatty acid (heptadecanoic acid, HA) of an administered triglyceride (triheptadecaenoin, THA). PA, the free fatty acid, is directly absorbed, while the THA must be hydrolyzed by pancreatic lipase for HA to be absorbed. The difference in patterns of absorption represented by the area under the curve (AUC) between the two provides insight into the pancreatic fat digestion and absorption capabilities [49]. The MBT can detect changes in fat absorption based on the timing of pancreatic enzyme administration [50]. This test was found to be more sensitive to fat maldigestion than CFA [51]. This test is not yet commercially available in the United States.

Direct Testing

While indirect tests are generally less invasive, direct tests may provide a more definitive assessment of pancreatic function. However, direct pancreatic function testing is less widely available, usually limited to dedicated pancreatic centers. Similar to some of the indirect tests, direct function tests and the literature supporting them is limited by inconsistent outcome measures, protocols, and cut-off points.

Endoscopic pancreatic function testing (ePFT) involves the direct collection via endoscopy of pancreatic fluid after administration of the secretagogues secretin and/or cholecystokinin (CCK): secretin stimulates ductal bicarbonate and fluid secretion, and CCK induces degranulation of pancreatic proenzymes from the acinar cells. The resulting secretions are collected from the duodenum at the ampulla of Vater using a sterile suction catheter under endoscopic guidance. Pancreatic fluid secretion typically begins 3–4 min after secretin administration, with optimal collection occurring within the first 10 min to ensure accurate enzyme activity measurements and bicarbonate concentrations reflecting ductal cell function. The pH, bicarbonate, protein content, amylase, lipase, trypsin, chymotrypsin, elastase, and other enzymes like carboxypeptidase can be assayed from the

collected fluid. Total protein and pH measurement during ePFT assess the quality of the assay; low protein concentration may indicate dilution with duodenal contents, while a pH < 7 suggests potential contamination with gastric fluid.

While direct testing via ePFT appears to provide an accurate assay of both ductal and acinar function, the test has significant limitations. Specific aspects of the protocol including the use and timing of administration of the secretagogue(s), timing of fluid collection(s), and enzymes assayed vary from center to center, potentially leading to variability in sensitivity, specificity, and reproducibility. While studies have demonstrated that using CCK alone produces comparable enzyme activity as CCK and secretin combined – suggesting this approach maintains accuracy testing acinar function – bicarbonate concentrations have not been assessed in this manner to evaluate ductal function [52]. Opioid, benzodiazepine, and anticholinergic medications can influence test results. The test is invasive, requiring sedation or general anesthesia. Finally, while ePFT is well-established in adults, normative values for pediatric populations, particularly for peak fluid, enzyme, and bicarbonate secretions, have yet to be fully validated. International organizations have called for centers performing ePFT to adhere to a standardized protocol to increase the utility of the test [53].

Imaging, while primarily assessing the anatomical structure of the pancreas, can offer insight into exocrine function. Secretin-enhanced magnetic resonance cholangiopancreatography, S-MRCP, is one such technique that evaluates pancreatic fluid secretion in response to secretin. Trout et al. measured secreted fluid in 50 children and reported a correlation between the secreted volume and body surface area of the pancreas. A secreted volume of less < 43 mL or secretion rate of < 2.3 mL/min was considered abnormal [54]. Similarly, endoscopic ultrasound is a highly accurate imaging technique used to visualize the pancreatic ducts and parenchyma. In patients with CP, the presence of pancreatic calcifications or ductal dilation may indicate EPI. In a study of 128 adult patients, the presence of pancreatic calcifications, duct dilation, and hyperechoic foci were independently associated with the presence of EPI. In a cohort of 539 patients with CP, small pancreatic size was associated with EPI [55].

Practical Clinical Approach

Ultimately, diagnosis of EPI relies on a high index of suspicion, careful history, and strategic testing. In some cases, a therapeutic PERT trial may be appropriate to confirm a diagnosis; this approach has gained support in recent years and is now regarded as standard practice [56]. However, this approach may present the clinician with a dilemma, as improvement in maldigestive symptoms may not be specific for EPI. Furthermore, the approach to EPI in adult and pediatric populations is necessarily different, as are the etiologies underlying EPI in these populations.

Unfortunately, strategic testing approaches integrating indirect and direct testing methods have not been deeply studied in either population. In general, an indirect method like FE-1 may be used to screen for EPI, while a direct test like ePFT may be used to detect more subtle variations in pancreatic function, differential ductal versus acinar origin of EPI, or detect isolated enzyme deficiencies. In patients with specific underlying conditions like CP, imaging may play a role as well. By combining these various diagnostic modalities, healthcare providers can more effectively identify EPI in at-risk populations.

Treating Exocrine Pancreatic Insufficiency

A management approach considering short- and long-term consequences of macronutrient and micronutrient deficits is necessary including effects on growth and weight gain, body composition, bone health, and symptoms related to micronutrient deficiencies. Finally, depending on the underlying etiology, the symptoms and adverse nutritional consequences of EPI may have significant negative impacts on quality of life. Treatments should be chosen in conjunction with the patient and/or caregiver with the ultimate goal of maximizing quality of life.

Consequences of EPI

Perhaps the most significant consequence of inadequate pancreatic enzyme activity in the intestinal lumen is dietary fat malabsorption. Maldigested fat in the lumen is responsible for the typical symptoms EPI including abdominal pain, bloating, and flatulence. In addition to causing symptoms and significantly reducing calorie and essential fatty acid (EFA) absorption, failure to hydrolyze triglycerides into free fatty acids reduces micelle formation and thus reduced absorption of the fat-soluble vitamins A, D, E and K. In patients with impaired ductal function or inadequate neutralization of gastric hydrochloric acid, absorption of dietary vitamin B12, calcium, zinc, and selenium may be impaired [1]. Protein and carbohydrate malabsorption can contribute to the overall calorie deficit and negative nitrogen balance, compounding malnutrition.

In the short term, dietary fat malabsorption results in acute symptoms related to steatorrhea and poor weight gain or weight loss. Over time, the associated calorie deficit may cause muscle wasting and malnutrition, and children may demonstrate linear growth failure. Fat-soluble vitamin and

EFA deficiencies may accrue over time and contribute to decreased bone density [57].

Pancreatic Enzyme Replacement Therapy

The mainstay of EPI treatment is pancreatic enzyme replacement therapy (PERT), the exogenous provision of pancreatic enzymes to digest one or all of the macronutrient components in the diet. The majority of PERT formulations in 2025 contain combinations of lipase, amylase, and protease in varying doses to ease administration. Compensatory mechanisms such as salivary amylase and gastric peptidase can compensate for the loss of pancreatic amylase and protease; however, the human body does not have a mechanism to salvage loss of pancreatic lipase, and thus PERT focuses primarily on fat absorption and lipase activity. The primary form of lipase in most formulations is pancrelipase extracted from porcine pancreatic tissue, relevant for patients with dietary restrictions forbidding the consumption of pork products. A recombinant, yeast-derived formulation, adrulipase, was safe and effective but failed to significantly improve the CFA in a majority of subjects in a recent Phase 2 clinical trial (NCT link).

Most PERT formulations are enteric-coated to prevent denaturing in the acidic environment of the stomach, releasing the active enzyme only when exposed to the more basic environment in the small intestine. A non-coated formulation is available and used frequently in patients who require enteral formula. An enteric feeding in-line cartridge (EFIC) containing a recombinant, bacterial-derived lipase is available for patients requiring enteral feeds as well; despite containing only lipase, its use is associated with improved growth parameters [58].

While PERT improves dietary fat absorption, it by itself does not completely normalize fat absorption or improve fat-soluble vitamin status [59]. Even with some residual fat malabsorption, PERT has been shown in patients with CP and EPI to mitigate weight loss as well as improve associated symptoms such as increased stool frequency, abdominal pain, and flatulence [60, 61]. Appropriate PERT dosing is also associated with improvement in QOL and normalization of eating habits in patients with pancreatic cancer [62].

PERT dosage varies by age, EPI severity, and fat content of the meal. Most professional guidelines provide recommendations based on studies in patients with cystic fibrosis and EPI, presented in Table 2 [56]. Historically, the ideal adult dose has been estimated at 10% of the normal pancreatic lipase production with each meal, a concentration associated with adequate fat and fat-soluble vitamin absorption to prevent deficiency, around 90,000 units of exogenous lipase per meal. Pediatric doses are weight-based and vary by age, though dietary fat content may be considered when assessing the patient's response to PERT. In both adult and pediatric patients, the snack dose is approximately half the meal dose [1]. For children who are unable to swallow a capsule, enzyme beads may be sprinkled on a small amount of applesauce or other acidic food. Children who have prolonged mealtimes may also benefit from a split dose with the first half administered at the beginning of a meal and the second half administered thirty minutes into the meal.

Enteral PERT administered with tube feeds may be dosed based on patient weight, fat content of the formula, or volume of formula administered, depending on the formulation. Patients may consume enteric PERT orally prior to g-tube feeds at standard doses (see Table 2). If a patient is unable to consume PERT orally and the non-enteric coated enzyme formulation is used, it is dosed between 500 and 4000 lipase units per gram of fat in the feed. If a patient is unable to consume PERT orally and the EFIC is used, one cartridge should be used for every 500mL of formula for a maximum of six cartridges/day.

Successful treatment of EPI with PERT varies depending on the patient's clinical situation at the start of therapy, their underlying disease process, and goals of treatment. In the United States there is currently little value in repeating malabsorptive stool testing after starting PERT due to limited reliability and applicability. The ^{13}C mixed-triglyceride breath test and the malabsorption blood test have demonstrated utility in evaluating PERT response, but neither is widely available [51, 63]. In general, experts agree that symptomatic relief and correction of nutritional deficiencies are reasonable treatment goals. Patients who do not appear to respond to PERT initially or after dose escalation should prompt the clinician to consider additional factors as outlined in Table 3.

Ultimately, other etiologies for maldigestive symptoms or malnutrition must be considered. Notably in patients with CP, up to 40% of patients may have small intestinal bacterial overgrowth (9598808). Ultimately, the decision whether to continue to use PERT in light of limited efficacy rests with the treating clinician and the patient/caregiver; the burden

Table 2 Dosing recommendations for pancreatic enzyme replacement therapy

Age	Initial dose	Titration
< 12 months	1000–2500 LU/kg/feed	Increase by 1 capsule per dose based on clinical symptoms to max of: – 2,500 LU/kg/meal – 10,000 LU/kg/day
1–4 years	Meals: 1000–2500 LU/kg Snacks: 500–1250 LU/kg	
≥4 years	Meals: 500–2500 LU/kg Snacks: 250–1250 LU/kg	
Adults	Meals: 40,000–50,000 LU Snacks: 20,000–25,000 LU	

LU lipase units

Table 3 Factors to consider when troubleshooting inadequate response to pancreatic enzyme replacement therapy (PERT)

Dose optimization	An increase in PERT dose may be warranted.
Adherence	- PERT should be taken just prior to eating - PERT should be available at meals in all settings (home, work, school, etc.) - Cost may impact adherence - Literacy may impact adherence
Storage	- Extreme temperatures may inactivate PERT (Ex: low temps in a cooler with food, high temps in a car's glove box) - Exposure to extreme temperatures during mail delivery are possible. - Enzymes may not be stable past their expiration date.
Acid suppression	- PERT is denatured in an acidic environment, it is reasonable to consider a trial of acid-suppressing therapy as an adjunct to PERT in the setting of an incomplete response.

associated with PERT use should be weighed against its lack of efficacy.

Macronutrient and Micronutrient Optimization

The importance of a holistic approach to treating EPI with a combination of PERT and appropriate dietary fat intake to optimize fat absorption was established in the late 1980's in a seminal study comparing two approaches to treating patients with CF and EPI. Patients treated with a higher-fat, higher-calorie diet in addition to standard PERT dosing demonstrated superior linear growth, weight gain, and life expectancy when compared to patients treated with a lower-fat diet with less PERT dosing [64]. Subsequent practice for management of EPI regardless of the underlying etiology has emphasized maintaining adequate fat and calorie intake to prevent malnutrition-related morbidity and mortality. To that end, consultation with a dietitian and systematic follow-up are necessary.

Prior to the EPI diagnosis, patients may minimize dietary fat intake to reduce maldigestive symptoms associated with steatorrhea. Dietary fat intake < 10 g/day in adults without EPI is associated with essential fatty acid and fat-soluble vitamin deficiencies. Thus, it is important to screen for these deficiencies at diagnosis to facilitate timely intervention and correction of any deficiencies. Parenteral fat-soluble vitamin preparations are not currently available in the United States, but enteral water-miscible preparations are available.

A lysophosphatidylcholine-rich structured lipid product is available in the United States with micelle-like activity that improves dietary essential fat and fat-soluble vitamin absorption independent of pancreatic lipase [65, 66]. Such a product presents an alternative or adjunct to PERT in patients who may not tolerate it or have otherwise restricted diets.

Conclusion

EPI is caused by a variety of conditions that differ along the age spectrum. The lack of clear clinical criteria and reliable non-invasive testing make diagnosis challenging. A high index of suspicion based on clinical history should inform testing and potentially a therapeutic trial of PERT. Providers should thus be familiar with conditions that predispose to EPI. Once EPI is diagnosed, PERT should be started and anthropometric and biochemical nutritional status should be monitored regularly. If a patient does not respond to PERT, other etiologies for maldigestion should be investigated.

Key References

- De Rijk FEM, van Veldhuisen CL, Besselink MG, van Hooft JE, van Santvoort HC, van Geenen EJM, et al. Diagnosis and treatment of exocrine pancreatic insufficiency in chronic pancreatitis: An international expert survey and case vignette study. Pancreatology. 2022 May;22 [4]:457 − 65.

  This survey emphasizes the current variations in practice regarding diagnosis and management of EPI even among leading pancreatologists worldwide. Multiple case vignettes are included that have excellent educational value.

- Chu P, Mioc J, Henry O, O'Donovan P. The clinical, economic, and humanistic burden of treatments for exocrine pancreatic insufficiency and cost-effectiveness of treatments: A systematic literature review. Medicine (Baltimore). 2024 Aug 16;103 [6]:e39224.

  This systematic review illustrates the negative impact EPI has on quality of life as well as increased treatment costs. It also demonstrates that EPI often does this as a comorbid condition to other diseases.

- Landers A, Donaldson F, Brown H, McKenzie C, Pendharkar S. The Impact of Pancreatic Enzyme Replacement Therapy on Patients With Advanced Pancreatic Adenocarcinoma: A Systematic Review and Narrative Synthesis. Pancreas. 2022 May 1;51 [40]:405–14.

  A review of PERT use in patients with pancreatic cancer that emphasizes the multiple potential benefits as well as highlighting the general lack of awareness.

- Di Martino M, de la Hoz Rodriguez Á, Saibanti A, Salvador Camarmo G, Pagano N, Martín-Pérez E, et al. Pancreatic exocrine insufficiency after pancreatic resection: a systematic review. BMC Surg. 2025 Feb 3;25 [1]:53.

  Article highlighting the paucity of data supporting the use of fecal elastase-1 to diagnose EPI in patients who have undergone pancreatic resection (and thus other etiologies aside from cystic fibrosis). In addition, summarizes the potential impacts on pancreatic function after resection.

Author Contributions A.B. and J.N.B. wrote the main manuscript text. A.M. prepared Table 1. All authors participated in review and revision of the manuscript, agree the work is ready for submission, and accept responsibility for the contents.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests Dr Stallings has a non-financial interest: She is currently an unpaid medical consultant with Solace Nutrition, LLC, which licenses and manufactures the structured lipid Encala. She has potential to receive royalties and/or consulting feeds in the future. Dr Stallings and Dr Brownell have a non-financial interest: They both contributed to the development of the malabsorption blood test along with other investigators at CHOP; however, the test is not licensed for commercial use, and they do not stand to receive any financial benefit if the test were to be used commercially.

References

1. Brownell JN, Bashaw H, Stallings VA. Growth and nutrition in cystic fibrosis. Semin Respir Crit Care Med. 2019;40(6):775–91.
2. de la Iglesia-Garcia D, Vallejo-Senra N, Iglesias-Garcia J, López-López A, Nieto L, Domínguez-Muñoz JE. Increased risk of mortality associated with pancreatic exocrine insufficiency in patients with chronic pancreatitis. J Clin Gastroenterol. 2018;52(8):e63-72.
3. Partelli S, Frulloni L, Minniti C, Bassi C, Barugola G, D'Onofrio M, et al. Faecal elastase-1 is an independent predictor of survival in advanced pancreatic cancer. Dig Liver Dis. 2012;44(11):945–51.
4. Chu P, Mioc J, Henry O, O'Donovan P. The clinical, economic, and humanistic burden of treatments for exocrine pancreatic insufficiency and cost-effectiveness of treatments: A systematic literature review. Med (Baltim). 2024;103(33):e39224.
5. Singh VK, Schwarzenberg SJ. Pancreatic insufficiency in cystic fibrosis. J Cyst Fibros. 2017;16(Suppl 2):S70–8.
6. Ramsey ML, Li SS, Lara LF, Gokun Y, Akshintala VS, Conwell DL, et al. Cystic fibrosis transmembrane conductance regulator modulators and the exocrine pancreas: a scoping review. J Cyst Fibros. 2023;22(2):193–200.
7. Thompson AS, Giri N, Gianferante DM, Jones K, Savage SA, Alter BP, et al. Shwachman diamond syndrome: narrow genotypic spectrum and variable clinical features. Pediatr Res. 2022;92(6):1671–80.
8. Uc A, Fishman DS. Pancreatic disorders. Pediatr Clin North Am. 2017;64(3):685–706.
9. Ellery KM, Erdman SH. Johanson-Blizzard syndrome: expanding the phenotype of exocrine pancreatic insufficiency. JOP. 2014;15(4):388–90.
10. Wolters-Eisfeld G, Mercanoglu B, Hofmann BT, Wolpers T, Schnabel C, Harder S, et al. Loss of complex O-glycosylation impairs exocrine pancreatic function and induces MODY8-like diabetes in mice. Exp Mol Med. 2018;50(10):1–13.
11. Tjora E, Wathle G, Erchinger F, Engjom T, Molven A, Aksnes L, et al. Exocrine pancreatic function in hepatocyte nuclear factor 1β-maturity-onset diabetes of the young (HNF1B-MODY) is only moderately reduced: compensatory hypersecretion from a hypoplastic pancreas. Diabet Med. 2013;30(8):946–55.
12. Keogh SJ, McKee S, Smithson SF, Grier D, Steward CG. Shwachman-Diamond syndrome: a complex case demonstrating the potential for misdiagnosis as asphyxiating thoracic dystrophy (Jeune syndrome). BMC Pediatr. 2012;12:48.
13. Tumino M, Meli C, Farruggia P, La Spina M, Faraci M, Castana C, et al. Clinical manifestations and management of four children with pearson syndrome. Am J Med Genet A. 2011;155A(12):3063–6.
14. Hopson P, Patel S, Bornstein J, Mehta D, Horvath K. Isolated amylase deficiency in children and its clinical implication. J Pediatr Gastroenterol Nutr. 2019;68(6):854–60.
15. Hildebrand H, Borgström B, Békássy A, Erlanson-Albertsson C, Helin I. Isolated co-lipase deficiency in two brothers. Gut. 1982;23(3):243–6.
16. Ligumsky M, Granot E, Branski D, Stankiewicz H, Goldstein R. Isolated lipase and colipase deficiency in two brothers. Gut. 1990;31(12):1416–8.
17. Ghishan FK, Moran JR, Durie PR, Greene HL. Isolated congenital lipase-colipase deficiency. Gastroenterology. 1984;86(6):1580–2.
18. Li Y, Li R, Pan Y, Zhou W, Wang X, Dong L, et al. Enterokinase deficiency associated with novel TMPRSS15 gene mutations: a case report. Front Pediatr. 2025;13:1484208.
19. Ghishan FK, Lee PC, Lebenthal E, Johnson P, Bradley CA, Greene HL. Isolated congenital enterokinase deficiency. Recent findings and review of the literature. Gastroenterology. 1983;85(3):727–31.
20. Hardt PD, Ewald N. Exocrine pancreatic insufficiency in diabetes mellitus: a complication of diabetic neuropathy or a different type of diabetes? Exp Diabetes Res. 2011;2011:761950.
21. Lankisch PG, Manthey G, Otto J, Koop H, Talaulicar M, Willms B, et al. Exocrine pancreatic function in insulin-dependent diabetes mellitus. Digestion. 1982;25(3):211–6.
22. Gröger G, Layer P. Exocrine pancreatic function in diabetes mellitus. Eur J Gastroenterol Hepatol. 1995;7(8):740–6.
23. Nell S, Borel Rinkes IHM, Verkooijen HM, Bonsing BA, van Eijck CH, van Goor H, et al. Early and late complications after surgery for MEN1-related nonfunctioning pancreatic neuroendocrine tumors. Ann Surg. 2018;267(2):352–6.

24. Ros-Pérez P, Golmayo L, Cilleruelo ML, Gutiérrez C, Celaya P, Lacámara N, et al. Octreotide-related exocrine pancreatic insufficiency (EPI) in congenital hyperinsulinism. J Pediatr Endocrinol Metab. 2020;33(7):947–50.
25. Arya VB, Senniappan S, Demirbilek H, Alam S, Flanagan SE, Ellard S, et al. Pancreatic endocrine and exocrine function in children following near-total pancreatectomy for diffuse congenital hyperinsulinism. PLoS One. 2014;9(5):e98054.
26. Cade A, Walters M, Puntis JW, Arthur RJ, Stringer MD. Pancreatic exocrine and endocrine function after pancreatectomy for persistent hyperinsulinaemic hypoglycaemia of infancy. Arch Dis Child. 1998;79(5):435–9.
27. Salvatore S, Finazzi S, Barassi A, Verzelletti M, Tosi A, Melzi d'Eril GV, et al. Low fecal elastase: potentially related to transient small bowel damage resulting from enteric pathogens. J Pediatr Gastroenterol Nutr. 2003;36(3):392–6.
28. Garah J, Rosen I, Shaoul R. Transient exocrine pancreatic insufficiency in children: an existing entity? J Pediatr Gastroenterol Nutr. 2019;68(4):574–7.
29. Liu QY, Abu-El-Haija M, Husain SZ, Barth B, Bellin M, Fishman DS, et al. Risk factors for rapid progression from acute recurrent to chronic pancreatitis in children: report from INSPPIRE. J Pediatr Gastroenterol Nutr. 2019;69(2):206–11.
30. Jiang C, Barkin JA, Barkin JS. Exocrine pancreatic insufficiency is common in Celiac disease: a systematic review and meta-analysis. Dig Dis Sci. 2023;68(8):3421–7.
31. Kunovský L, Dítě P, Jabandžiev P, Eid M, Poredská K, Vaculová J, et al. Causes of exocrine pancreatic insufficiency other than chronic pancreatitis. J Clin Med. 2021;10(24):5779.
32. Martín-de-Carpi J, Moriczi M, Pujol-Muncunill G, Navas-López VM. Pancreatic involvement in pediatric inflammatory bowel disease. Front Pediatr. 2017;5:218.
33. Fernandez J, Hopson P, Patel SB, Horvath K, Pandey A. Prevalence of exocrine pancreatic dysfunction based on direct function testing in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2023;76(4):475–9.
34. Di Martino M, de la Hoz Rodriguez Á, Saibanti A, Salvador Camarmo G, Pagano N, Martín-Pérez E, et al. Pancreatic exocrine insufficiency after pancreatic resection: a systematic review. BMC Surg. 2025;25(1):53.
35. Zoppi G, Andreotti G, Pajno-Ferrara F, Njai DM, Gaburro D. Exocrine pancreas function in premature and full term neonates. Pediatr Res. 1972;6(12):880–6.
36. Boehm G, Bierbach U, Senger H, Jakobsson I, Minoli I, Moro G, et al. Postnatal adaptation of lipase- and trypsin-activities in duodenal juice of premature infants appropriate for gestational age. Biomed Biochim Acta. 1990;49(5):369–73.
37. Yang Y, Sanchez D, Figarella C, Lowe ME. Discoordinate expression of pancreatic lipase and two related proteins in the human fetal pancreas. Pediatr Res. 2000;47(2):184–8.
38. Fomon SJ, Ziegler EE, Thomas LN, Jensen RL, Filer LJ. Excretion of fat by normal full-term infants fed various milks and formulas. Am J Clin Nutr. 1970;23(10):1299–313.
39. Löhr JM, Panic N, Vujasinovic M, Verbeke CS. The ageing pancreas: a systematic review of the evidence and analysis of the consequences. J Intern Med. 2018;283(5):446–60.
40. de Rijk FEM, van Veldhuisen CL, Besselink MG, van Hooft JE, van Santvoort HC, van Geenen EJM, et al. Diagnosis and treatment of exocrine pancreatic insufficiency in chronic pancreatitis: an international expert survey and case vignette study. Pancreatology. 2022;22(4):457–65.
41. Katschinski M, Schirra J, Bross A, Göke B, Arnold R. Duodenal secretion and fecal excretion of pancreatic elastase-1 in healthy humans and patients with chronic pancreatitis. Pancreas. 1997;15(2):191–200.
42. Whitcomb DC, Buchner AM, Forsmark CE. AGA clinical practice update on the epidemiology, evaluation, and management of exocrine pancreatic insufficiency: expert review. Gastroenterology. 2023;165(5):1292–301.
43. Bashaw H, Brownell JN, Schall JI, Stallings VA. Measures of dietary fat and energy absorption in healthy adults. Pancreas. 2020;49(6):845–54.
44. Caras S, Boyd D, Zipfel L, Sander-Struckmeier S. Evaluation of stool collections to measure efficacy of PERT in subjects with exocrine pancreatic insufficiency. J Pediatr Gastroenterol Nutr. 2011;53(6):634–40.
45. Hopson P, Smadi Y, Mehta V, Patel S, Mehta D, Horvath K. Assessment of exocrine pancreatic function in children and adolescents with direct and indirect testing. Front Pediatr. 2022;10:908542.
46. Green MR, Austin S, Weaver LT. Dual marker one day pancreolauryl test. Arch Dis Child. 1993;68(5):649–52.
47. Domínguez-Muñoz JE, Nieto L, Vilariño M, Lourido MV, Iglesias-García J. Development and diagnostic accuracy of a breath test for pancreatic exocrine insufficiency in chronic pancreatitis. Pancreas. 2016;45(2):241–7.
48. Powell-Brett S, Hall LA, Roberts KJ. A standardised nutritional drink as a test meal for the 13 C mixed triglyceride breath test for pancreatic exocrine insufficiency: a randomised, two-arm crossover comparative study. J Hum Nutr Diet. 2024;37(1):137–41.
49. Mascarenhas MR, Mondick J, Barrett JS, Wilson M, Stallings VA, Schall JI. Malabsorption blood test: assessing fat absorption in patients with cystic fibrosis and pancreatic insufficiency. J Clin Pharmacol. 2015;55(8):854–65.
50. Stallings VA, Mondick JT, Schall JI, Barrett JS, Wilson M, Mascarenhas MR. Diagnosing malabsorption with systemic lipid profiling: pharmacokinetics of pentadecanoic acid and triheptadecanoic acid following oral administration in healthy subjects and subjects with cystic fibrosis. Int J Clin Pharmacol Ther. 2013;51(4):263–73.
51. Brownell JN, Schall JI, Stallings VA. Pancreatic function in chronic pancreatitis: a cohort study comparing 3 methods of detecting fat malabsorption and the impact of short-term pancreatic enzyme replacement therapy. Pancreas. 2019;48(8):1068–78.
52. Pfefferkorn MD, Fitzgerald JF, Croffie JM, Gupta SK, Caffrey HM. Direct measurement of pancreatic enzymes: a comparison of secretagogues. Dig Dis Sci. 2002;47(10):2211–6.
53. Patel N, Sellers ZM, Grover A, Liu QY, Maqbool A, Morinville VD, et al. Endoscopic pancreatic function testing (ePFT) in children: A position paper from the NASPGHAN pancreas committee. J Pediatr Gastroenterol Nutr. 2021;72(1):144–50.
54. Trout AT, Serai SD, Fei L, Sun Q, Abu-El-Haija M. Prospective assessment of normal pancreatic secretory function measured by MRI in a cohort of healthy children. Am J Gastroenterol. 2018;113(9):1385.
55. Nordaas IK, Trelsgård AM, Tjora E, Frøkjær JB, Haldorsen IS, Olesen SS, et al. Pancreatic atrophy is a predictor for exocrine pancreatic dysfunction: data from a large cohort of patients with chronic pancreatitis. Pancreatology. 2024;24(8):1244–51.
56. Dominguez-Muñoz JE, Vujasinovic M, de la Iglesia D, Cahen D, Capurso G, Gubergrits N, et al. European guidelines for the diagnosis and treatment of pancreatic exocrine insufficiency: UEG, EPC, EDS, ESPEN, ESPGHAN, ESDO, and ESPCG evidence-based recommendations. United Eur Gastroenterol J. 2025;13(1):125–72.
57. Gupta M, Midha S, Sachdeva V, Singh J, Pandey S, Mittal C, et al. Subclinical pancreatic exocrine insufficiency is associated with osteopathy in patients with chronic pancreatitis: implications for management. Pancreatology. 2025;25(2):193–9.
58. Shrivastava S, Shaw K, Lee M, Reitich P, Hunter S, Klosterman M, et al. Association of in-line digestive enzyme cartridge with

enteral feeds on improvement in anthropometrics among pediatric patients with cystic fibrosis. Nutr Clin Pract. 2024;39(4):903–10.
59. Kuhn RJ, Gelrud A, Munck A, Caras S. CREON (Pancrelipase Delayed-Release Capsules) for the treatment of exocrine pancreatic insufficiency. Adv Ther. 2010;27(12):895–916.
60. D'Haese JG, Ceyhan GO, Demir IE, Layer P, Uhl W, Löhr M, et al. Pancreatic enzyme replacement therapy in patients with exocrine pancreatic insufficiency due to chronic pancreatitis: a 1-year disease management study on symptom control and quality of life. Pancreas. 2014;43(6):834–41.
61. Kempeneers MA, Ahmed Ali U, Issa Y, van Goor H, Drenth JPH, van Dullemen HM, et al. Natural course and treatment of pancreatic exocrine insufficiency in a nationwide cohort of chronic pancreatitis. Pancreas. 2020;49(2):242–8.
62. Landers A, Donaldson F, Brown H, McKenzie C, Pendharkar S. The impact of pancreatic enzyme replacement therapy on patients with advanced pancreatic adenocarcinoma: a systematic review and narrative synthesis. Pancreas. 2022;51(5):405–14.
63. Domínguez-Muñoz JE, Iglesias-García J, Vilariño-Insua M, Iglesias-Rey M. 13 C-mixed triglyceride breath test to assess oral enzyme substitution therapy in patients with chronic pancreatitis. Clin Gastroenterol Hepatol. 2007;5(4):484–8.
64. Corey M, McLaughlin FJ, Williams M, Levison H. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. J Clin Epidemiol. 1988;41(6):583–91.
65. Stallings VA, Schall JI, Maqbool A, Mascarenhas MR, Alshaikh BN, Dougherty KA, et al. Effect of oral lipid matrix supplement on fat absorption in cystic fibrosis: a randomized placebo-controlled trial. J Pediatr Gastroenterol Nutr. 2016;63(6):676–80.
66. Tindall A, Mascarenhas M, Maqbool A, Stallings VA. Lysophosphatidylcholine-rich nutrition therapy increased gut absorption of coingested dietary fat: a randomized controlled trial. Curr Dev Nutr. 2023;7(9):101985.