AGA Clinical Practice Update on the Epidemiology, Evaluation, and Management of Exocrine Pancreatic Insufficiency: Expert Review

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DESCRIPTION: Exocrine pancreatic insufficiency (EPI) is a disorder caused by the failure of the pancreas to deliver a minimum/threshold level of specific pancreatic digestive enzymes to the intestine, leading to the maldigestion of nutrients and macronutrients, resulting in their variable deficiencies. EPI is frequently underdiagnosed and, as a result, patients are often not treated appropriately. There is an urgent need to increase awareness of and treatment for this condition. The aim of this American Gastroenterological Association (AGA) Clinical Practice Update Expert Review was to provide Best Practice Advice on the epidemiology, evaluation, and management of EPI. **METHODS:** This Expert Review was commissioned and approved by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee (CPUC) and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the CPUC and external peer review through standard procedures of *Gastroenterology*. These Best Practice Advice statements were drawn from a review of the published literature and from expert opinion. Because systematic reviews were not performed, these Best Practice Advice statements do not carry formal ratings regarding the quality of evidence or strength of the presented considerations.

BEST PRACTICE ADVICE STATEMENTS

BEST PRACTICE ADVICE 1: EPI should be suspected in patients with high-risk clinical conditions, such as chronic pancreatitis, relapsing acute pancreatitis, pancreatic ductal adenocarcinoma, cystic fibrosis, and previous pancreatic surgery. **BEST PRACTICE ADVICE 2:** EPI should be considered in patients with moderate-risk clinical conditions, such as duodenal diseases, including celiac and Crohn's disease; previous intestinal surgery; longstanding diabetes mellitus; and hypersecretory states (eg, Zollinger–Ellison syndrome). **BEST PRACTICE ADVICE 3:** Clinical features of EPI include steatorrhea with or without diarrhea, weight loss, bloating, excessive flatulence, fat-soluble vitamin deficiencies, and protein-calorie malnutrition. **BEST PRACTICE ADVICE 4:** Fecal elastase test is the most appropriate initial test and must be performed on a semi-solid or solid stool specimen. A fecal elastase level <100 μg/g of stool provides good evidence of EPI, and levels of 100–200 μg/g are indeterminate for EPI. **BEST PRACTICE ADVICE 5:** Fecal elastase testing can be performed while on pancreatic enzyme replacement therapy. **BEST PRACTICE ADVICE 6:** Fecal fat testing is rarely needed and must be performed when on a high-fat diet. Quantitative testing is generally not practical for routine clinical use. **BEST PRACTICE ADVICE 7:** Response to a therapeutic trial of pancreatic enzymes is unreliable for EPI diagnosis. **BEST PRACTICE ADVICE 8:** Cross-sectional imaging methods (computed tomography scan, magnetic resonance imaging, and endoscopic ultrasound) cannot identify EPI, although they play an important role in the diagnosis of benign and malignant pancreatic disease. **BEST PRACTICE ADVICE 9:** Breath tests and direct pancreatic function tests hold promise, but are not widely available in the United States. **BEST PRACTICE ADVICE 10:** Once EPI is diagnosed, treatment with pancreatic enzyme replacement therapy (PERT) is required. If EPI is left untreated, it will result in complications related to fat malabsorption and malnutrition, having a negative impact on quality of life. **BEST PRACTICE ADVICE 11:** PERT formulations are all derived from porcine sources and are equally effective at equivalent doses. There is a need for H2 or proton pump inhibitor therapy with non–enteric-coated preparations. **BEST PRACTICE ADVICE 12:** PERT should be taken during the meal, with the initial treatment of at least 40,000 USP units of lipase during each meal in adults and one-half of that with snacks. The subsequent dosage can be adjusted based on the meal size and fat content. **BEST PRACTICE ADVICE 13:** Routine supplementation and monitoring of fat-soluble vitamin levels are appropriate. Dietary modifications include a low-moderate fat diet with frequent smaller meals and avoiding very-low-fat diets. **BEST PRACTICE ADVICE 14:** Measures of successful treatment with PERT include reduction in steatorrhea and associated gastrointestinal symptoms; a gain of weight, muscle mass, and muscle function; and improvement in fat-soluble vitamin levels. **BEST PRACTICE ADVICE 15:** EPI should be monitored and baseline measurements of nutritional status should be obtained (body mass index, quality-of-life measure, and fat-soluble vitamin levels). A baseline dual-energy x-ray absorptiometry scan should be obtained and repeated every 1–2 years.

Exocrine pancreatic insufficiency (EPI) is caused by the failure of the pancreas to deliver a threshold level of pancreatic digestive enzymes to the intestine to

digest meals and meet nutritional and metabolic needs. The threshold is dependent on specific macro- and micronutritional needs; nutrient intake; exocrine pancreatic function, and intestinal anatomy, function, intestinal diseases, and adaptative capacity.[1]

Clinically, EPI is characterized by variable deficiencies in micro- and macronutrients, especially essential fats and fat-soluble vitamins; gastrointestinal symptoms of nutrient maldigestion; and improvement with lifestyle changes, disease treatment, optimized diet, dietary supplements, and/or administration of adequate pancreatic enzyme replacement therapy (PERT) (Figure 1A and B).[1]

There is an urgent need for best practice updates to increase awareness of this condition and the importance of its adequate treatment. This review discusses the proposed Best Practice Advice statements, which should be used in conjunction with evolving literature as part of a shared decision-making process.

Best Practice Advice 1: EPI should be suspected in patients with high-risk clinical conditions, such as chronic pancreatitis (CP), relapsing acute pancreatitis (AP), pancreatic ductal adenocarcinoma, cystic fibrosis, and previous pancreatic surgery.

EPI develops in more than one-half of patients with CP, and the risk depends on the disease's duration, stage, and etiology.[2,3] Chronic alcohol use, smoking, pancreatic ductal obstruction, atrophy, duct calcifications, and diabetes mellitus[4] increase the likelihood of EPI in CP, and in patients with these features or etiologies, the risk of EPI is >80%. EPI typically occurs after 5–10 years of the disease.[5] Abstinence from smoking and alcohol may delay the onset of EPI. In AP and relapsing AP, the pooled prevalence during follow-up ranges from 27% to 62%, and the rate appears to be similar for both AP and recurrent AP.[6,7] Autoimmune pancreatitis is often associated with EPI.[8] Most patients with cystic fibrosis will have EPI presenting at birth or in infancy (85%).

EPI is common in patients with pancreatic ductal adenocarcinoma due to obstruction of the main pancreatic duct with upstream atrophy and the effects of chemotherapy, radiation therapy, and/or surgery.[9,10] The rates of EPI in unresectable pancreatic ductal adenocarcinoma range from 50% to 92%, 40%–50% in resectable pancreatic ductal adenocarcinoma before treatment, and 75% after treatment.[9,11] Surgical resection of the pancreas of any type predisposes to EPI.[12] Ampullary cancer and main duct intraductal papillary mucinous neoplasm can also produce EPI by obstructing the pancreatic duct (Table 1).

Best Practice Advice 2: EPI should be considered in patients with moderate-risk clinical conditions, such as duodenal diseases, including celiac and Crohn's disease; previous intestinal surgery; long-standing diabetes mellitus; and hypersecretory states (eg, Zollinger–Ellison syndrome).

Digestion of nutrients by pancreatic digestive enzymes requires stimulation of pancreatic secretion, delivery of the enzymes to the intestine, and sufficient dwell time in a suitable environment to hydrolyze the nutrients for absorption. In patients without an underlying pancreatic disease, other diseases of the gastrointestinal tract may occasionally overlap with and mimic EPI.[13] The stomach and

duodenum are sensory organs that activate the pancreas. Injury to the duodenal mucosa, as in untreated celiac disease, diminishes stimulation of pancreatic secretion and impairs the absorption of micronutrients, lipids, fat-soluble vitamins, and vitamin B12.[1,13] Elevated duodenal acid, as in Zollinger–Ellison syndrome, may lead to EPI from the destruction of pancreatic enzymes by acid.[13]

Surgery to remove or bypass portions of the stomach, duodenum, and jejunum may result in EPI.[1,14,15] EPI is also common with loss of the pylorus, with dumping syndrome and various motility disorders causing asynchrony (delivery of enzymes not matching delivery of the meal in the upper intestine) (Table 1).[16]

Insulin is a trophic factor for pancreatic acinar cells and diabetes may impact the risk of developing EPI. Long-standing diabetes mellitus type 1 diminishes pancreatic digestive enzyme secretion and fecal human elastase-1 (FE-1) levels, but does not cause EPI alone.[17,18] In CP, EPI is more frequent in patients who also have diabetes.[4,19] Of note, diabetes may also occur after AP and CP due to typical type 2[20] or to loss of pancreatic islets from pancreatitis, including both α (glucagon) and β (insulin) cells (called type 3c diabetes mellitus).[21,22]

Best Practice Advice 3: Clinical features of EPI include steatorrhea with or without diarrhea, weight loss, bloating, excessive flatulence, fat-soluble vitamin deficiencies, and protein-calorie malnutrition.

As a syndrome, EPI is a combination of signs and symptoms (Table 2). In CP, EPI develops gradually over time, so clinical signs and symptoms may initially be few and mild compared with late-stage CP.[23] The intestinal effects are due to microbial digestion of unabsorbed nutrients, and the systemic effects are due to micro- and macronutrient maldigestion and malabsorption. Deficiencies in levels of vitamins A, D, E, and K are most common,[24,25] but deficiencies of other vitamins and trace elements can also be seen.[24] Osteoporosis and bone fracture,[26,27] weight loss, sarcopenia,[28,29] reduced quality of life,[30] higher rates of surgical complications,[29] and an increase in mortality are common systemic complications.[31]

The differential diagnosis for EPI is broad and multiple disorders may be present in the same patient, making diagnosis challenging. EPI-specific patient-reported outcome measures have been developed but cannot distinguish EPI from other causes of similar symptoms.[23,32,33] Common diseases with symptoms that overlap with EPI include celiac disease[34]; small intestinal bacterial overgrowth[35,36]; long-standing diabetes mellitus; and inflammatory bowel diseases, such as Crohn's disease.[1,37] Less common causes include disaccharidase deficiencies[38,39]; bile acid diarrhea[40]; and infectious etiologies, such as giardiasis.[41] These are most often considered when a patient with EPI does not respond to PERT.

Best Practice Advice 4: Fecal elastase test is the most appropriate initial test and must be performed on a semi-solid or solid stool specimen. A fecal elastase level <100 μg/g of stool provides good evidence of EPI, while levels of 100–200 μg/g of stool are indeterminate for EPI.

Pancreatic function tests are objective, quantitative measures of exocrine pancreatic or ductal synthetic and
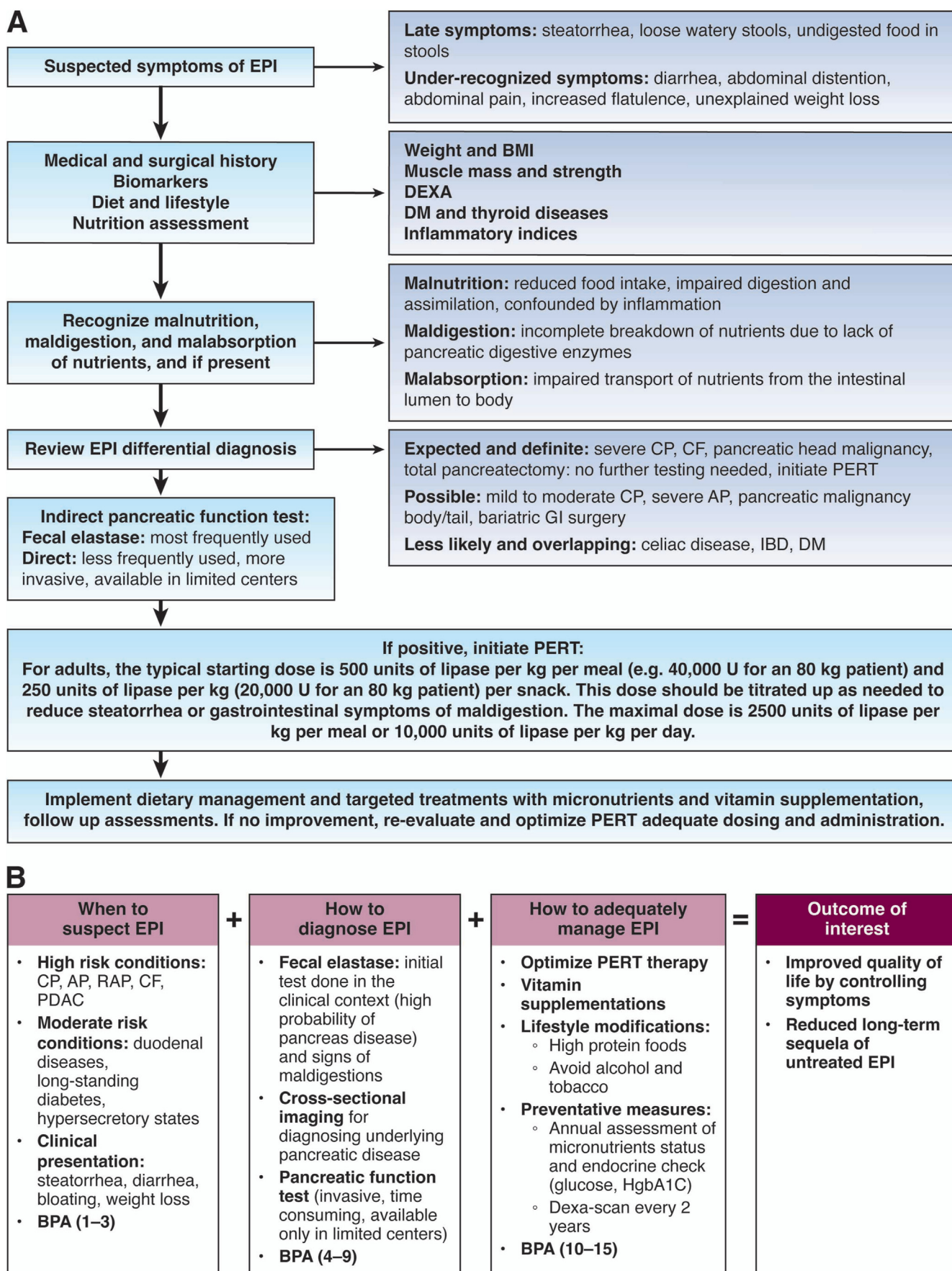
A

| Suspected symptoms of EPI | → | **Late symptoms:** steatorrhea, loose watery stools, undigested food in stools

Under-recognized symptoms: diarrhea, abdominal distention, abdominal pain, increased flatulence, unexplained weight loss |

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| Medical and surgical history
Biomarkers
Diet and lifestyle
Nutrition assessment | → | **Weight and BMI**
Muscle mass and strength
DEXA
DM and thyroid diseases
Inflammatory indices |

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| Recognize malnutrition, maldigestion, and malabsorption of nutrients, and if present | → | **Malnutrition:** reduced food intake, impaired digestion and assimilation, confounded by inflammation

Maldigestion: incomplete breakdown of nutrients due to lack of pancreatic digestive enzymes

Malabsorption: impaired transport of nutrients from the intestinal lumen to body |

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| Review EPI differential diagnosis | → | **Expected and definite:** severe CP, CF, pancreatic head malignancy, total pancreatectomy: no further testing needed, initiate PERT

Possible: mild to moderate CP, severe AP, pancreatic malignancy body/tail, bariatric GI surgery

Less likely and overlapping: celiac disease, IBD, DM |

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Indirect pancreatic function test:
Fecal elastase: most frequently used
Direct: less frequently used, more invasive, available in limited centers

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If positive, initiate PERT:
For adults, the typical starting dose is 500 units of lipase per kg per meal (e.g. 40,000 U for an 80 kg patient) and 250 units of lipase per kg (20,000 U for an 80 kg patient) per snack. This dose should be titrated up as needed to reduce steatorrhea or gastrointestinal symptoms of maldigestion. The maximal dose is 2500 units of lipase per kg per meal or 10,000 units of lipase per kg per day.

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Implement dietary management and targeted treatments with micronutrients and vitamin supplementation, follow up assessments. If no improvement, re-evaluate and optimize PERT adequate dosing and administration.

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When to suspect EPI	+	How to diagnose EPI	+	How to adequately manage EPI	=	Outcome of interest

• **High risk conditions:** CP, AP, RAP, CF, PDAC
• **Moderate risk conditions:** duodenal diseases, long-standing diabetes, hypersecretory states
• **Clinical presentation:** steatorrhea, diarrhea, bloating, weight loss
• BPA (1–3)
		• **Fecal elastase:** initial test done in the clinical context (high probability of pancreas disease) and signs of maldigestions
		• **Cross-sectional imaging** for diagnosing underlying pancreatic disease
		• **Pancreatic function test** (invasive, time consuming, available only in limited centers)
		• BPA (4–9)
				• **Optimize PERT therapy**
				• **Vitamin supplementations**
				• **Lifestyle modifications:**
				  ◦ High protein foods
				  ◦ Avoid alcohol and tobacco
				• **Preventative measures:**
				  ◦ Annual assessment of micronutrients status and endocrine check (glucose, HgbA1C)
				  ◦ Dexa-scan every 2 years
				• BPA (10–15)
						• **Improved quality of life by controlling symptoms**
						• **Reduced long-term sequela of untreated EPI**

Figure 1. (*A*) Approach to suspected EPI. (*B*) Approach to EPI. BPA, Best Practice Advice; CF, cystic fibrosis; PDAC, pancreatic ductal adenocarcinoma; RAP, recurrent acute pancreatitis.

Table 1. Exocrine Pancreatic Insufficiency Types, Pathomechanisms, and Examples of Conditions

EPI type	Pathomechanism	Examples of conditions
Loss of pancreatic parenchyma	Reduced pancreatic enzymes synthesis and secretion Reduced bicarbonate delivery	Pancreatic cancer CP Cystic fibrosis Pancreatic resection
Other causes	Obstruction of pancreatic duct Reduced pancreatic enzymes delivery Reduced bicarbonate delivery	Ampullary tumors Ductal stenosis Pancreatic cancer
	Reduced endogenous stimulation (reduced CCK-mediated secretion, Reduced enterokinase (pro-enzyme not converted to active enzymes)	Duodenal resection Enteropathies (eg, Crohn's disease, celiac disease) Somatostatinomas
	Decreased pancreatic enzymes activity in the small bowel	Inadequate mixing of pancreatic enzymes in the bile (dumping syndrome) Postcibal asynchrony (short gut syndrome, gastric resection) Intraluminal inactivation (hypersecretary states, gastrinoma Surgery reconstructions

secretory activity. Direct measurements of pancreatic secretions into the duodenum are the most accurate, but are invasive, time-consuming, and a more significant burden to the patient than an indirect test.[1,4,42] Direct pancreatic function tests are available at some specialized centers using endoscopic methods.[43,44] The most recent methods include stimulating the pancreas and aspirating pancreatic secretions for 30–60 minutes, with the juice analyzed for bicarbonate concentration and pancreatic digestive enzymes. These tests are used most commonly for diagnosing early-stage CP rather than as a diagnostic test for EPI.

The most used indirect pancreatic function test is the FE-1 because it is simple, noninvasive, and relatively inexpensive.[45–47] This pancreatic enzyme is best at surviving intestinal passage so that stool levels can be an indirect measure of pancreatic digestive enzyme production. The test can distinguish normal, moderate, and severe EPI under controlled conditions. An FE-1 value of <200 μg/g of stool is considered abnormal, with levels <100 μg/g of stool is more consistent with EPI.[48] Some investigators suggest that the FE-1 value of <50 μg/g is most reliable for severe EPI.[49]

The limitation of the FE-1 test is that it is insensitive to mild EPI.[48] The test is most accurate when analyzing formed or semi-formed stool. Clinicians should be aware that in the setting of very watery stools, the FE-1 can be diluted and may be falsely abnormal. It is susceptible to false-positive results, especially in settings where the prevalence of EPI is low.[1] It may be repeated if the results are indeterminate, especially if there is evidence of pancreatic disease and a high probability of EPI. Patient compliance with collecting and mailing their stool to an office or laboratory is often low. In patients with a high pretest probability of EPI (eg, steatorrhea in a patient with a known pancreatic disease) treatment with PERT can be initiated without FE-1 testing. In those with these underlying pancreatic conditions but no

symptoms, measurement of FE-1 to help confirm EPI is appropriate.

Best Practice Advice 5: Fecal elastase testing can be performed while on pancreatic enzyme replacement therapy.

The FE-1 test was designed in part to overcome the problem of the fecal chymotrypsin test that cross-reacted with chymotrypsin in PERT.[50] The commonly used ScheBo Pancreatic Elastase 1 Stool Test (ScheBo Biotech AG,

Table 2. Clinical Symptoms of Exocrine Pancreatic Insufficiency

Symptoms

Gastrointestinal effects (microbial digestion of unabsorbed nutrients)
    Bloating
    Borborygmi
    Flatulency
    Osmotic diarrhea
    Steatorrhea

Nutritional systemic effects
    Micronutrients (fat-soluble vitamin deficiency A, D, E, K, vitamin B12, essential fatty acid malabsorption)
        Visual problems, night blindness (vitamins A, E, B12)
        Skin rash (vitamin A, B12, essential fatty acids)
        Osteoporosis, osteopenia (vitamin D)
        Neurologic effects (vitamin E, B12)
        Coagulopathy (vitamin E)
        Anemia (vitamin B12)
        Fatigue, weakness (vitamin E, B12)
        Depression (vitamin D, B12)
    Macronutrients (protein maldigestion, food avoidance)
        Unintendedly weight loss
        Sarcopenia

Giessen, Germany) measures chymotrypsin-like elastases 3A and 3B, as humans do not secrete elastase-1.[51]

Measuring serum pancreatic enzyme levels (eg, trypsin) as an alternative indirect pancreatic function test also has the advantage of not being affected by PERT. These tests are unreliable if the patient has ongoing pancreatic inflammation.[4,52,53]

Exogenous PERT use does not alter FE-1 test results, and repeat FE-1 measurements are not helpful for assessing treatment response.

Best Practice Advice 6: Fecal fat testing is rarely needed and must be performed on a high-fat diet. Quantitative testing is generally not practical for routine clinical use.

Steatorrhea is the cardinal clinical feature of EPI and has been defined as a coefficient of fat absorption of <93% (>7% of ingested fat is present in the stool). The presence of visible steatorrhea usually requires moderate fat in the diet. A formal quantitative test requires a diet of known fat content ingested over 5 days and collection of stool for fat measurement over the course of the final 3 days. The test is burdensome, difficult to implement, and rarely performed outside clinical research. Stool fat measures, including Sudan stain, are nonspecific for EPI.[54] Stool fat measurement can be considered when clinical features are inconclusive, to determine the presence of steatorrhea, or when assessing an inadequate clinical response to PERT.

Best Practice Advice 7: Response to a therapeutic trial of pancreatic enzymes is unreliable for EPI diagnosis.

PERT is effective for treating EPI (below). Patients with nonspecific symptoms, such as bloating, excess gas, and foul-smelling or floating stools may note some improvement in these symptoms while taking PERT, but these symptoms are nonspecific and symptomatic changes may be a placebo effect or masking other disorders, such as celiac disease, causing delays in a correct diagnosis. Appropriate testing (eg, fecal elastase) is suggested before initiating therapy with PERT.

Best Practice Advice 8: Cross-sectional imaging (computed tomography scan, magnetic resonance imaging, and endoscopic ultrasound) cannot identify EPI, although they play an important role in the diagnosis of benign and malignant pancreatic disease.

When EPI is suspected, cross-sectional imaging is commonly done to evaluate the pancreas for any underlying pancreatic abnormalities, including pancreatic neoplasia, that may support an EPI diagnosis. Cross-sectional images demonstrating end-stage calcific pancreatitis or significant pancreatic atrophy correlate with the presence of EPI.[55] Normal pancreatic imaging also correlates with the absence of EPI.[55] Although there is an association between EPI and advanced CP defined by atrophy and dense calcifications,[4] there is no correlation for more moderate pancreatic imaging changes seen on computed tomography,[4] magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography,[56] or endoscopic ultrasound findings.[57,58] Secretin-enhanced MRI retrograde cholangiopancreatography is a valuable tool for visualization of ductal anatomy, including pancreas divisum, anomalous pancreaticobiliary junction, and postsurgical anatomy,[59] but there is not a close correlation between secretin-enhanced MRI retrograde cholangiopancreatography and EPI. Newer imaging techniques may improve the predictive value of abdominal imaging for EPI, including endoscopic ultrasound elastography[60] and new MRI measures using pancreas-to-spleen T1 signal intensities and extracellular volume fraction.[56] Although current cross-sectional imaging techniques cannot accurately predict EPI, they remain useful biomarkers of pancreatic disease pathology and a central part of overall patient evaluation.

Best Practice Advice 9: Breath tests and direct pancreatic function tests hold promise, but are not widely available in the United States.

EPI can be diagnosed indirectly by demonstrating diminished fat digestion in the intestine. Breath tests were developed to measure intestinal digestion of mixed triglycerides in which the carbons are radiolabeled with ^{13}C or ^{14}C.[61,62] These isotope-labeled triglycerides are digested by pancreatic lipase and co-lipase, and the $^{13}CO_2$ or $^{14}CO_2$ are released, exhaled, and measured in expired breath. Digestion in humans takes time, hence a collection of breath over many hours is needed. This approach has the advantage over other commonly used tests in that it directly measures pancreatic enzyme–specific digestion.[61,62] $^{14}CO_2$ is easy to measure but is radioactive. Although it has the advantage of not being radioactive, measuring ^{13}C requires mass spectrometry. This technique is more widely used in Europe, where methods between countries are now harmonized.[63]

An alternative approach developed in the United States is to deliver an oral substrate that is digested and used to measure the products of digestion in the blood. One test uses a naturally occurring fatty acid (absorbed without the need for enzymes) and a triglyceride (which requires lipase to release the fatty acid). The ratio of the 2 fatty acids in the blood provides a measure of pancreatic enzyme–specific digestion.[64,65] Similar to the breath test, the blood test takes many hours of sample collection.

Both tests measure digestive activity rather than enzyme quantity. These can be repeated on PERT therapy to measure efficacy.

Best Practice Advice 10: Once EPI is diagnosed, treatment with PERT is required. If EPI is left untreated, it will result in complications related to fat malabsorption and malnutrition, having a negative impact on quality of life.

Once EPI is diagnosed, a multidisciplinary evaluation is helpful to establish the state of the patient's digestive and endocrine systems.[1,66] This includes a dietary assessment from a certified dietitian, if available, to determine nutritional needs and specific deficits (eg, vitamins A, D, E, K, and B12, selenium, unintentional weight loss, protein balance, and caloric needs) plus dietary adjustments based on needs and comorbidities (eg, diabetes mellitus, dyslipidemia, celiac disease, CFTR-related disorder, prior surgery, and cancer therapy).[66,67] Coordination of care with an endocrinologist is warranted if there is prediabetes or diabetes. Finally, lifestyle patterns that affect pancreatic and nutritional

health, such as smoking and excess alcohol consumption, should be addressed.[67] Although useful for treating pain, endoscopic or surgical pancreatic ductal drainage procedures are not effective in preventing or improving EPI.

The adverse sequelae of EPI are summarized in Table 2. The use of PERT in patients with CP and EPI improves outcomes.[30] PERT is also an essential part of managing EPI and nutrition in the setting of cystic fibrosis.[68,69]

In patients with pancreatic cancer, EPI is associated with reduced quality of life and survival and a reduced ability to tolerate medical and surgical oncologic therapy.[10] In patients with pancreatic cancer after pancreatoduodenectomy, the use of PERT appears to improve outcomes.[70] Failure to properly provide PERT in adequate doses results in a continuation of maldigestion symptoms, micro- or macronutritional deficiencies, poor quality of life, and increased mortality.[1,31]

Best Practice Advice 11: Once EPI is diagnosed, treatment with PERT is required. If EPI is left untreated, it will result in complications related to fat malabsorption and malnutrition, having a negative impact on quality of life.

Currently, all commercially available products are of porcine origin and labeled based on their USP lipase content (Table 3). The preparations include lipase, amylase, and a mixture of proteases. One preparation is available as non–enteric-coated tablets (Viokace); the remainder are capsules containing micropellets of enzymes in a pH-sensitive polymer. The non–enteric-coated preparation requires cotreatment with an acid-reducing agent to prevent acid denaturing of lipase and other digestive enzymes. Acid-reducing agents are not required for those on enteric-coated preparations, although most of these patients are also on a proton pump inhibitor or H2-blocker for other reasons, such as improving PERT efficacy.[71] The drugs are equipotent at similar lipase dosages, and there is generally no reason to switch from one to another based on response. Switching agents may be required depending on the pharmaceutical benefit plan, as the out-of-pocket costs can be quite substantial. In those that lack drug coverage, the cost of these products may make it difficult for patients to obtain them even with patient-assistance programs available through the manufacturers.

Over-the-counter commercially available pancreas enzyme replacements should not be used, as they are classified as dietary supplements only. The dosing and efficacy of over-the-counter enzymes are neither standardized nor regulated, and thus utility and safety are unknown.

Best Practice Advice 12: PERT should be taken during the meal, with the initial treatment of at least 40,000 USP units of lipase during each meal in adults and one-half of that with snacks. The subsequent dosage can be adjusted based on the meal size and fat content.

PERT treats the meal, not the pancreas. Thus, it must be taken during the meal to maximize mixing and digestion of nutrients.[72,73] Humans have other mechanisms for protein and carbohydrate digestion, but not fats,[1] so the focus of PERT is on lipase dose and meal fat content. The primary goal is to ensure adequate digestion of lipids to meet macro-

and micronutritional needs, with a secondary goal to reduce steatorrhea and intestinal symptoms that may be diet-related (eg, large, high-fat meals).

A normal pancreas makes approximately 900,000 USP units of lipase during an average meal, with approximately 90,000 units of lipase needed to prevent steatorrhea (10% of normal). Even at high doses, PERT formulations are not as efficient as normal pancreatic secretion and do not correct steatorrhea entirely.[72,73] Most patients have some residual pancreatic function, so 40,000–50,000 USP units of lipase is a reasonable initial dosage and one-half that amount with snacks.[1,45,46,66,74] The dosage can be adjusted (up for larger meals or meals with higher fat content and down for smaller or low-fat meals). Doses >120,000 USP units of lipase per meal are seldom required. For children and adults with advanced CP, as in cystic fibrosis, the typical starting dose is 500 units of lipase per kg per meal (eg, 40,000 units for an 80-kg patient) and 250 units of lipase per kg (20,000 units for an 80-kg patient) per snack.[75] This dose should be titrated as needed to reduce steatorrhea or gastrointestinal symptoms of maldigestion. The maximum dose for cystic fibrosis is <10,000 units of lipase per kilogram body weight per day; or <4000 units per gram of dietary fat per day.[75] Monitoring stool frequency and visible steatorrhea, weight, fat-soluble vitamin levels, and muscle strength and function provide useful information on the adequacy of PERT therapy. Adverse effects, such as nausea, abdominal cramping, bloating, diarrhea, and constipation, may occur with PERT. Rare adverse effects include fibrosing colonopathy, allergic reactions to the porcine proteins, and hyperuricosuria. No nonporcine products are currently available, but are being developed. PERT therapy is generally lifelong, although dosage adjustments and even reductions can be considered in patients who are doing well and have acceptable nutritional parameters.

Prescription PERT can be very expensive, especially when higher doses are required. Because this can be an essential part of management, lower cost and/or better insurance coverage are needed, especially for low-income patients.

Best Practice Advice 13: Routine supplementation and monitoring of fat-soluble vitamin levels are appropriate. Dietary modifications include a low-moderate fat diet with frequent smaller meals and avoiding very-low-fat diets.

Digestion of fats is one of the central roles of pancreatic digestive enzyme secretion that cannot be compensated for by adaptation or optimization of other parts of the diet and digestive system. Patients may adopt a very-low-fat diet to avoid fat maldigestion symptoms. However, this approach may lead to deficiencies of essential fatty acids and the fat-soluble vitamins A, D, E, and K.[25,76,77] Screening for vitamin and mineral deficiencies (vitamins A, D, E, K, B12, folate, magnesium, selenium zinc, and iron studies) at the time of diagnosis and then annually based on the clinical status of the patient, remains essential.

The use of vitamin supplements significantly increases vitamin levels in patients with CP.[25] Vitamin deficiencies in African American people are significantly worse for vitamin D, α-tocopherol, and retinal binding protein.[25] Deficiencies of

Table 3. US Food and Drug Administration–Approved Formulations of Pancreatic Enzyme Replacement Therapy

Brand	Type	Available lipase strengths (USP)
Creon	Enteric-coated microspheres	3,000/6,00/12,000/24,000/36,000
Zenpep	Enteric-coated beads	3,000/5,000/10,000/15,000/20,000/25,000/40,000
Pancreaze	Enteric-coated microtablets	2,600/4,200/10,500/16,800/21,000/37,00
Pertzye	Enteric-coated microspheres	4,000/8,000/16,000/24,000
Viokace	Non–enteric-coated tablets	10,444/20,880
Relizorb	In-line lipase cartridge	For enteral feedings formulas

vitamins D and K are associated with osteopathy and fractures in CP,[78,79] and treatment reduces bone fracture rates.[80]

Best Practice Advice 14: Measures of successful treatment with PERT include reduction in steatorrhea and associated gastrointestinal symptoms; a gain of weight, muscle mass, and muscle function; and improvement in fat-soluble vitamin levels.

The treatment response to PERT should be measured to ensure that adequate doses are being taken, that they are taken correctly, and to assess the need for prescribing H2 receptor antagonist or proton pump inhibitors.[66,67] The frequency of follow-up assessment depends on the timing of the initiation of treatment and the dynamics of the patient's condition. Stable patients should have the state of pancreatic disease and treatment effectiveness assessed at least annually.[1,66,67] Lifestyle modifications along with adequate PERT and vitamin supplementation include the consumption of frequent small, high-protein content meals with avoidance of alcohol and tobacco.

Best Practice Advice 15: EPI should be monitored and baseline measurements of nutritional status should be obtained (body mass index, quality-of-life measure, and fat-soluble vitamin levels). A baseline dual-energy x-ray absorptiometry scan should be obtained and repeated every 1–2 years.

Monitoring nutritional status is essential in those with EPI, as in all other conditions associated with malnutrition. Important measures include anthropomorphic (height, weight, handgrip strength, muscle mass [eg, computed tomography or other techniques], and body mass index), serum biomarkers, and clinical assessment (eg, physical activity, diet, alcohol use, smoking, sitophobia, abdominal pain [primarily related to meals], bloating, bowel habits, and steatorrhea).[67] Patients with EPI of any etiology may be obese and still have sarcopenia. Other muscle mass and function assessments can also be considered (eg, psoas muscle size at L3 level or simple tests, such as a timed up-and-go test).[28,81]

In those with CP, obtaining baseline measurements of symptoms and quality of life can also be useful in assessing the effectiveness of therapy. In stable patients, annual measurements of fat-soluble vitamins and serum markers of malnutrition (eg, prealbumin and retinol-binding protein), B12, folate, thiamine, selenium, zinc, and magnesium with regular screening for diabetes with hemoglobin A1c levels are reasonable. Inflammatory markers, such as C-reactive protein (or C-reactive protein to albumin ratio[82]) reflect chronic low-grade inflammation and a catabolic state and can be informative as important markers of conditions leading to EPI, such as CP. Given the common occurrence of metabolic bone disease in CP,[27] a baseline bone density assessment using dual-energy x-ray absorptiometry is needed and should be repeated every 1–2 years.[66] The finding of osteopenia or osteoporosis should lead to appropriate calcium and vitamin D intake, regular weight-bearing exercises, and avoidance of alcohol and smoking. Baseline measures of nutritional status, as outlined above, should generally be repeated annually, and dual-energy x-ray absorptiometry scans should be repeated every 2 years.

Conclusions

This review summarizes the Best Practice Advice statements for diagnosing and managing EPI. It is essential to diagnose this condition early and initiate treatment as soon as the diagnosis is made, to reduce the long-term consequences of untreated EPI. The adequate implementation of PERT improves the quality of life by controlling symptoms and ultimately reduces patient mortality and morbidity. Despite severe outcomes, EPI management remains suboptimal, underscoring the importance of raising awareness in high-risk patients, developing better diagnostics tests, improving access to PERT for patients, and developing newer and more potent agents. All efforts should be made to make PERT available and affordable to all patients with EPI. Effective management of patients with EPI requires broader implementation of diagnostic tools and treatment optimization.

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