

# Romanian Guidelines on the Diagnosis and Treatment of Exocrine Pancreatic Insufficiency

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## ABSTRACT

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In assessing exocrine pancreatic insufficiency (EPI), its diverse etiologies and the heterogeneous population affected should be considered. Diagnosing this condition remains a challenge in clinical practice especially for mild-to-moderate EPI, with the support of the time-consuming breath test or the coefficient of fat absorption. The fecal elastase-1 test, less precise for the diagnosis, cannot be useful for assessing treatment efficacy. Pancreatic enzyme replacement therapy (PERT) is the mainstay of treatment, whereby enteric-coated mini-microspheres are taken with every meal, in progressive doses based on an individual's weight and clinical symptoms. The main indication for PERT is chronic pancreatitis, in patients who have clinically relevant steatorrhea, abnormal pancreatic function test or abnormal function tests associated with symptoms of malabsorption such as weight loss or meteorism. While enzyme replacement therapy is not recommended in the initial stages of acute pancreatitis, pancreatic exocrine function should be monitored for at least 6-18 months. In the case of unresectable pancreatic cancer, replacement enzyme therapy helps to maintain weight and improve overall quality of life. It is also indicated in patients with celiac disease, who have chronic diarrhea (in spite of gluten-free diet), and in patients with cystic fibrosis with proven EPI.

**Key words:** exocrine pancreatic insufficiency – enzyme replacement therapy – chronic pancreatitis – guidelines.

**Abbreviations:** APPR: Romanian Association for Pancreatic Pathology; CAN: coefficient of nitrogen absorption; CCK: cholecystokinin; CF: cystic fibrosis; CFA: coefficient of fat absorption; <sup>13</sup>C-MTGT: <sup>13</sup>C-mixed triglyceride breath test; EPI: exocrine pancreatic insufficiency; FE-1 test: fecal elastase-1 test; QoL: quality of life; PERT: Pancreatic enzyme replacement therapy; PPI-proton pump inhibitor; RCT: randomized controlled trial.

## INTRODUCTION

This medical position statement developed by the Romanian Association for Pancreatic Pathology (APPR) encompasses the main diseases associated with exocrine pancreatic insufficiency (EPI), defined as an inadequate pancreatic enzyme activity to digest food generally due to either insufficient enzyme production, insufficient enzyme activation, or to early enzyme degradation. Recognition of this condition helps avoiding malnutrition-related morbidity and mortality, along with impaired quality of life (QoL) associated with low body mass index.

## METHODS

A Pubmed literature search was performed using the key words “exocrine pancreatic insufficiency”, “diagnosis”, “pancreatic enzyme replacement therapy”, “secretin”, “fecal elastase test” and “breath test”. A total of 2,632 manuscripts were retrieved, 132 of which met the inclusion criteria for analysis. The evidence and recommendations were discussed between the APPR participants using Oxford evidence criteria [1] and were reviewed and approved by independent experts.

## SEARCH RESULTS

### Whom to test for EPI

Chronic pancreatitis develops EPI when destruction of the pancreatic parenchyma is 90%, and it is aggravated by ductal obstruction caused by stricture or stones. The probability of exocrine insufficiency increases with disease duration and it occurs more rapidly in alcohol-related pancreatitis. More than half of the patients with alcohol-associated chronic pancreatitis

present EPI in 10 years after diagnosis and almost all after 20 years [2]. In autoimmune pancreatitis patients, EPI occurs in 80% of cases and improves under steroids [3].

Recovery of the pancreatic function after acute pancreatitis varies between three months and four years [3], but the severity of EPI is not directly related to the severity of the acute episode [4]. Pancreatic head tumors present with EPI at the diagnosis, and this aggravates in two months of evolution [5].

Pancreatectomy performed for pancreatic tumors is associated with EPI in about 70% of the cases [6], especially because duodenectomy diminishes the CCK release and induces an asynchronism between gastric emptying of the nutrients and the bilio-pancreatic secretion [7]. Stenosis of the pancreatic duct anastomosis aggravates pancreatic insufficiency [7, 8]. Distal pancreatectomy is transiently related to pancreatic insufficiency [8].

Celiac disease is associated with EPI in one third of the patients because of the reduced pancreatic stimulation [9].

Cystic fibrosis (CF) with duct obstruction is associated with EPI in 85% of the patients [10].

Exocrine pancreatic insufficiency is found in 30% of the patients with inflammatory bowel disease [11] and in association with autoimmune pancreatitis. It is present particularly in patients with loose stools, many stools/day and those with previous surgery; however, it is reversible in most patients [12].

Diabetes mellitus is associated with pancreatic atrophy due to the lack of the trophic insulin effects, and also due to diabetic enteropathy with the interruption of the entero-neuropathic reflexes or arteriopathy in type 2 diabetes. The prevalence of severe EPI was found to be 22% and it was higher in early onset of endocrine failure, long-lasting diabetes mellitus and low body mass index levels [13]. However, when alcohol intake was excluded, EPI occurred in only 5% of these patients [14].

Exocrine pancreatic insufficiency secondary to gastrointestinal Billroth II anastomosis or antrectomy is caused by

the dyssinergism between the pancreatic enzymes delivery and the food particles, the decrease of neuro-hormonal pancreatic stimulation, and the intestinal bacterial overgrowth [15].

### Diagnosis of EPI

The main clinical consequence of EPI is fat maldigestion and malabsorption resulting in steatorrhea. Patients have low circulating levels of micronutrients, fat soluble vitamins and lipoproteins. Various direct and indirect pancreatic function tests are available to diagnose EPI. Direct testing is the most sensitive one, but it is unpleasant for patients and is only used in specialized centers. Endoscopic function testing provides similar results to the standard secretin test, but takes about one hour to be performed and is rarely used [16]. Secretin-magnetic resonance pancreatography and secretin-endoscopic ultrasonography allow a quantitative assessment of pancreatic function, even in patients with a mild exocrine insufficiency, by assessing both duodenal filling and pancreatic ductal changes. These procedures are expensive, but they are considered as the most specific and sensitive tests for diagnosing EPI [17-19]. Indirect pancreatic function tests are non-invasive and assess the effects of pancreatic enzymes in the gastrointestinal tract such as undigested food or enzymes (e.g. stool human fecal elastase-1, FE-1).

Determination of FE-1 levels uses an enzyme-linked immunosorbent assay specific for this human protein. The normal value is >200 mg/g, and the lower the value is, the higher the probability of EPI [20]. Although generally pancreatic function testing requires discontinuation of PERT, FE-1 levels are not affected by pancreatic enzyme replacement therapy (PERT) so there is no indication to stop therapy. FE-1 has a better sensitivity (72%) for severe EPI [21] than for mild to moderate forms (sensitivity of 54%); test specificity is 79% for diagnosing mild to moderate EPI [22]. Its specificity is lower in cases of diarrhea, due to dilution [20], in diabetes [22] and isolated enzyme deficiencies [23].

The <sup>13</sup>C-mixed triglyceride test (<sup>13</sup>C-MTGT) is more extensively used for the diagnosis of EPI. The test sensitivity

**Table I.** Level of evidence (adapted from the modality of the Centre for Evidence Based Medicine, Oxford)[1]

Level of evidence	Type of evidence
1a	Systematic review of level 1b studies
1b	Individual randomized controlled trials (with narrow confidence interval)
2a	Systematic review of level 2b studies
2b	Individual cohort study (including low quality randomized controlled trials; e.g., <80% follow-up)
3a	Systematic review of case-control studies
3b	Individual case-control study
4	Case series
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
Grade of recommendation	
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

"Extrapolations" are where data is used in a situation that has potentially clinically important differences than the original study situation

for EPI is 90% [24]. The duration of the test (4 to 6 hours) is the major drawback. The test results could also be unreliable in case of intestinal malabsorption, severe liver disease and/or respiratory insufficiency.

### Indication for PERT

To avoid malnutrition-related morbidity and mortality in patients with chronic pancreatitis (CP), it is essential to start PERT as soon as EPI is diagnosed [25]. PERT improved pain and quality of life (QoL) for patients with pancreatic cancer in a multicenter observational study (n= 294) [26]. Improvement in the coefficient of fat absorption (CFA) and the coefficient of nitrogen absorption (CNA), as well as the stool aspect were noted in randomized controlled trials (RCTs) [27, 28].

Postoperative PERT has a positive impact on long-term patient survival after operative treatment for CP and should be the standard treatment at the time of hospital discharge, even when no clinical signs of EPI are present [29]. Cystic fibrosis is associated with a variable degree of pancreatic insufficiency in the first year following diagnosis, according to FE-1 [30]. PERT is associated with CFA and CNA improvement in RCTs of pediatric CF [31] and generally contributes to the increased survival in CF [32].

### Therapy

Therapeutic options include dietary measures, PERT, and treatment of the basic disease (pancreatic duct decompression).

**Table II.** Recommendation of the Romanian Association for the Pancreatic Pathology concerning the diagnosis and treatment of the exocrine pancreatic insufficiency

Indications for testing EPI		GR, LE
1. patients with loss of exocrine pancreatic tissue (primary EPI)	pancreatic cancer	B, 4
	chronic pancreatitis	A, 1b
	cystic fibrosis	A, 1b
	after acute necrotizing pancreatitis	C, 4
	after pancreatic resection	B, 4
2. pancreatic duct obstruction	ampullary tumors, pancreatic cancer	C, 4
3. inappropriate activation of the enzymes	celiac disease	C, 5
	inflammatory bowel disease, especially ileal Crohn's disease	C, 5
4. inactivation of the pancreatic enzymes	gastrinoma, somatostatinoma	D, 5
5. asynchronism	gastric surgery with Billroth II anastomosis	C, 4
	diabetes	
	short bowel syndrome	
<b>Diagnosis</b>		
No symptom definitively proves or excludes EPI.		A, 1b
Any time when there is the clinical suspicion, a pancreatic function test should be performed for identifying a subclinical EPI.		B, 1b
a. The secretin direct test, although standard for quantification of enzyme secretion, is not appropriate for EPI and is rarely used in practice.		A, 1b
b. Fecal elastase-1 measures pancreatic secretion and thus the probability of EPI.		B, 3b
c. Quantification of the coefficient of fat absorption (CFA) and the <sup>13</sup> C-MTG breath test are useful for diagnosing EPI, but their availability in clinical practice is limited.		C, 4
<b>Indication for PERT</b>		
1. Chronic pancreatitis. Patients who have:		
a. clinically relevant steatorrhea		A, 1b
b. abnormal pancreatic function test + clinical evidence of malabsorption, e.g., weight loss, meteorism		B, 2b
2. Acute pancreatitis		C, 3b
a. PERT not recommended during the initial stages of acute pancreatitis		
b. monitoring the EPI for at least 6–18 months and treating when abnormal test are noted.		
3. Unresectable pancreatic cancer. PERT helps to maintain weight and improve overall quality of life		B, 2b
4. Celiac disease patients with chronic diarrhea despite gluten free diet		C, 3b
5. Patients with cystic fibrosis, after diagnosis of EPI		A, 1b
<b>Management</b>		
Smoking and alcohol consumption should be stopped		A, 1b
The diet: normal-fat, well balanced, with micronutrients and individualized		D, 3b
Treatment with enteric-coated pH-sensitive mini-microspheres and with high lipase content		A, 1a
- The starting dose is of 40,000 IU of lipase per main meal and 10,000–25,000 lipase units for a snack		A, 1b
- Titration up based on weight gain and reduction of diarrhea and steatorrhea to ascertain the lowest effective dose		A, 1b
- When possible, the coefficient of fat absorption and breath test are useful for monitoring the treatment response		B, 1b
- Supplementation with fat-soluble vitamins is also appropriate		C, 3b
- Association with PPI or antiH2 medication for decreasing the intestinal pH is controversial		B, 2b

GR: grade of recommendation, LE: level of evidence, EPI: exocrine pancreatic insufficiency, PERT: pancreatic enzyme replacement therapy, PPI: proton pump inhibitor

### **Efficacy outcome measures**

The response to therapy is based on the coefficient of fat absorption, the results of the breath test and on the weight balance and the stool aspect.

The CFA is the current standard for evaluating PERT efficacy. Values < 93% in adults and < 85% in children aged <6 months are considered abnormal. The CNA test is a secondary outcome as a measure of protein digestion. Weight gain is a useful parameter to measure during long-term follow-up. Stool frequency and stool characteristics can be useful surrogates of the therapeutic outcome.

### **Dietary management for EPI**

The aim is to maintain an adequate intake and to correct nutritional deficiencies.

The diet to be followed in EPI is not specific but it should be well-balanced, with 35 kcal/kg body weight/day, 1-1.5 g/kg body weight/day of protein and 30% fat, rich in carbohydrates, low in fiber, sufficient to maintain the nutritional status [33, 34]. In order to improve energy and protein intake, the diet should be tailored to individual needs and micronutrient intake should be adequate. Patients with EPI should be encouraged to consume small, frequent meals and to abstain from alcohol. Low-fat diets are inferior in terms of total energy, and intake of fat-soluble vitamins is not recommended [35]. A normal fat diet is recommended. In the case of CF, a high fat diet is acceptable for nutritional goals in conjunction with appropriate enzyme supplementation [36]. In case of severe steatorrhea,

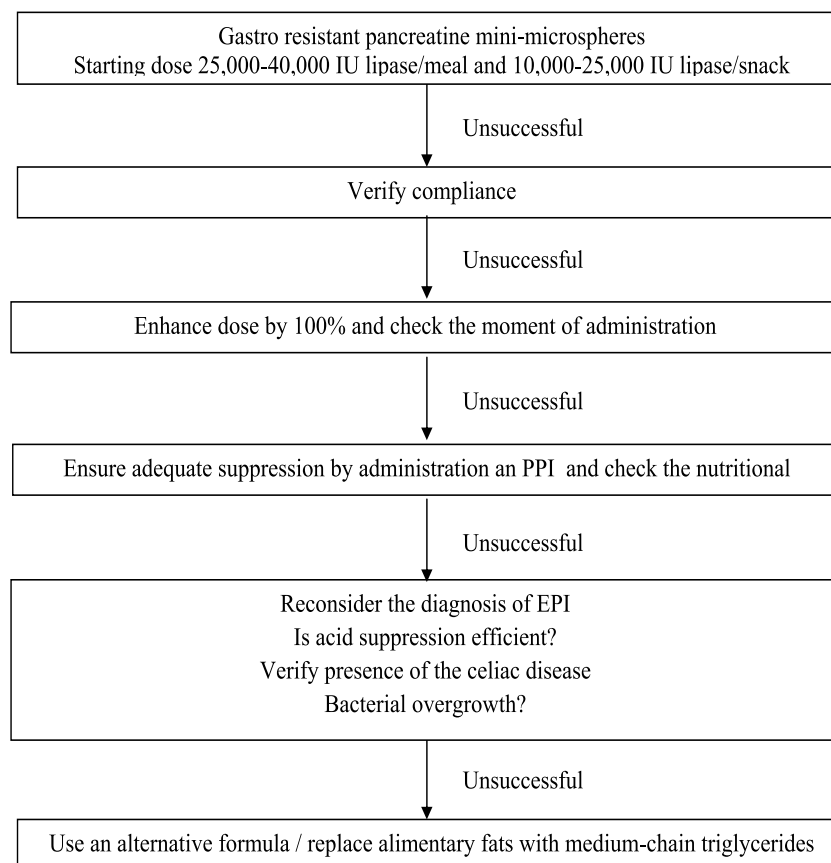
medium-chain triglycerides could be consumed in several (5-7) small meals, although this does not generally provide sufficient energy and it may also increase the risk of ketogenesis [37]. As the ingestion of fiber-rich foods including vegetables inhibits lipase activity by > 50%, a reduced fiber intake is considered beneficial in EPI [37].

### **PERT**

Pancreatic enzyme replacement therapy is the mainstay of EPI treatment. The objective is to deliver sufficient enzymatic activity into the duodenal lumen simultaneously with the meal in order to optimize digestion and absorption of nutrients.

Several RCTs have demonstrated that PERT improves fecal fat excretion in patients with EPI [26-28]. A systematic review of 12 RCTs demonstrated that PERT leads to significant reduction of fecal fat excretion versus placebo, but does not completely normalize fecal fat excretion [38]. The QoL may also be improved [39].

Key requirements for a pancreatic enzyme formula include high lipase activity, protection of the lipase from being destroyed by gastric acid, ease of mixing with the chyme (and exit from the stomach intact) and rapid release out of lipase from the protective enteric coating into the duodenum. Since the lipase of porcine pancreatin is destroyed by proteases and acids, protection from gastric acidity is essential. The best particle size for rapid release from the stomach through the pylorus is < 2mm in diameter, as these particles can exit the stomach with solid food.



**Fig. 1.** Management of the pancreatic enzyme replacement therapy (adapted from Pezzili [15] and de-Madeira [33]. PPI: proton pump inhibitors.

Current preparations contain porcine pancreatic extract encapsulated in micro-tablets or mini-microspheres with pH-sensitive enteric coating, as recommended by all major current European national consensus guidelines [18, 35, 40]. As exogenous enzymes should exert their action on the ingested meal and as gastric emptying of the enzymes should occur in parallel with nutrients in order to optimize digestion and absorption, PERT preparations should be given at every instance during a meal or snack, or at a short time after starting the meal/snack. This improves recovery rates as compared with preparations given before meals [41].

Appropriate doses for therapy start are 40,000 IU lipase/meal for CP or pancreatic surgery [35, 42], adjusted according to EPI severity, fat diet content, degree of symptom control, and maintenance of good nutritional status. They can be doubled or tripled based on the clinical need [42].

As a rule, lipase replacement is considered to be the most important component of PERT, and conversely, dosage of PERT is quantified as units of lipase as the most relevant measure of its clinical efficacy. This is due to the fact that even in case of complete absence of pancreatic exocrine secretion, > 80% digestion of starch and protein may be maintained by salivary, gastric and intestinal brush border enzymes, but failure of lipid digestion cannot be compensated [43].

#### **Side effects of PERT**

PERT is considered to have an acceptable safety and tolerability profile. For example, Kreon (Abbott Products GmbH Hannover, Germany) has an estimated cumulative post-marketing patient exposure since 14th April 1980 of about 5.9 million patient years [Personal communication: Dr. Julian Platon, Abbott, Addendum to Pancreatin Clinical Overview, 2014].

A maximum dose of 10,000 IU lipase/kg body weight is recommended [44]. Doses of 72,000 USP lipase/meal were associated with complication rates of 7.8%-13%, including abdominal pain, abdominal distension, and diarrhea [27], similar to placebo [28].

#### **Treatment failure**

When clinical steatorrhea or decreased nutritional status persist despite correct dosage, compliance and intestinal bacterial overgrowth should be checked [35]. Proton pump inhibitor (PPI) use is appropriate for non-enteric coated tablets. Recent guidelines still recommend PPI use in case of EPI resistant to treatment [35, 42].

## **CONCLUSIONS**

The recommendations formulated represent the consensus guiding the management of EPI and are based on clinical experience rather than clinical data. The suggested diagnostic tests are not compulsory when clinical suspicion exists and EPI is expected.

In assessing pancreatic exocrine function, its etiology should be considered. The EPI due to chronic pancreatitis, acute pancreatitis or upper gastrointestinal surgery increases the risk of poor nutrition, leading to complications and higher mortality. Weight loss negatively influences survival in patients with chronic pancreatitis and pancreatic cancer.

Diagnosis of EPI remains a challenge due to the lack of a reliable test available to identify mild-to-moderate forms of the condition. The FE-1 test, although well established, may not reliably measure mild-to-moderate EPI. The breath test is reliable for the diagnosis and for assessing treatment efficacy but it takes longer to perform. Pancreatic enzyme replacement treatment is the mainstay of EPI treatment.

Treatment with enteric-coated mini-microspheres is recommended at every meal, and progressively increasing doses may be given based on an individual's weight and clinical symptoms.

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