Guideline review

# Diagnosis and treatment of pancreatic exocrine insufficiency—European guidelines by UEG, EPC, EDS, ESPEN, ESPGHAN, ESDO and ESPCG

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/flgastro-2025-103247).

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Received 24 May 2025
Accepted 9 September 2025



**To cite:** Masegosa Ataz J, McCrudden R, Serrano Dueñas M, *et al*. *Frontline Gastroenterology* Epub ahead of print: [please include Day Month Year]. doi:10.1136/flgastro-2025-103247

## BACKGROUND

The relationship between low pancreatic enzyme output and malabsorption was described in 1973 in the *New England Journal of Medicine*.[1] Over the last four decades, different consensus groups, expert reviews and societal group recommendations have attempted to conceptualise this condition. Older guidelines addressed pancreatic exocrine insufficiency (PEI) as an enzymatic deficiency generally occurring in late pancreatic injury. In recent years, the concept of PEI as a multifaceted syndrome has emerged.[2]

### Concept and pathophysiology

For digestion to take place, concurrent stimulation of pancreatic secretion, chyme transit and enzymatic interaction are required. If this balance is impaired, maldigestion will occur and eventually symptoms of PEI can manifest.

In the new guidelines, PEI is described as a maldigestion syndrome caused by reduction in the exocrine pancreatic secretion and/or intraluminal activity of pancreatic enzymes below the level required for normal digestion. Historically, the emphasis was on low exocrine secretion due to pancreatic parenchymal damage and/or pancreatic ductal obstruction. However, the new guidelines acknowledge the importance of secondary mechanisms, such as impaired neurohormonal pancreatic stimulation, and also recognise the existence of pancreatic insufficiency despite the presence of overtly normal anatomical morphology and pancreatic function.

The physiology of pancreatic exocrine secretion includes vagal stimulation which begins during the cephalic phase and intensifies postprandially by gastric distention. Chemical stimulation occurs with acidic chyme (which promotes secretin release by duodenal S cells, activating bicarbonate release by pancreatic ductal cells) and fats and proteins (which promote duodenal I cell secretion of cholecystokinin to bolster enzymatic release by acinar cells). Pancreatic proteases are produced as inactive

### KEY POINTS

⇒ Pancreatic exocrine insufficiency (PEI) is a complex syndrome in which enzymatic activity is impaired causing clinical symptoms and deleterious effect on nutrition.
⇒ Faecal elastase is useful for screening high-risk populations but warrants careful interpretation in lower risk individuals.
⇒ Faecal elastase in isolation cannot confirm or rule out PEI and requires clinical context. In high likelihood individuals, confirmation may not be needed to start treatment.
⇒ Pancreatic enzyme replacement therapy (PERT) is known to improve nutritional status, symptoms and quality of life and may improve survival.
⇒ Patients should be regularly monitored for clinical and nutritional response, adherence to PERT, retesting in certain settings and alternative diagnosis sought when response is insufficient.

precursors: conversion of trypsinogen (precursor) to trypsin by enteropeptidase (brush border enzyme) needs to occur as the first step in the proteolytic cascade. Trypsin acts as a protease itself and cleaves other pancreatic zymogens into their active forms. Pancreatic lipase is activated by the lipid-water interface provided by bile salt fat emulsification, colipase for stabilisation and calcium ions. Amylase activity requires specific conditions such as calcium ions and high pH.

Given the need for multiple complex mechanisms to function harmoniously, there are many scenarios where normal enzymatic and bicarbonate secretion can still associate reduced activity. Factors like altered vagal and hormonal postprandial stimulation (which may occur after gastrointestinal or pancreatic surgery) can affect food transit coordination (asynchrony), reducing intraluminal protease activation and the mixing of pancreatic enzymes with chyme. Pancreatic enzymes are inactivated at pH values below 4, which can occur in hyperacidic environments or when bicarbonate secretion is not sufficient to buffer luminal pH conditions. Damaged or atrophic duodenal mucosa, for example, in coeliac disease, can result in loss of enteroendocrine cells or brush border enzymes leading to a defective regulation of pancreatic secretion or impaired proteolytic cascade, respectively.

### Diagnosis

The presence of symptoms, impaired nutrition and loss of pancreatic function all point to a diagnosis of PEI (see figure 1). Symptoms of PEI are non-specific; therefore, careful history taking is essential. Features include steatorrhoea, diarrhoea, flatulence and weight loss. Symptoms develop when pancreatic secretion is significantly reduced and/or the compensatory elements (ie, salivary amylase, gastric pepsin and lipase, intestinal disaccharidases or gastrointestinal motility) are lost. It should be recognised that many patients may experience an asymptomatic reduction in pancreatic secretion so long as output remains sufficient to maintain adequate nutrition. This should be labelled as exocrine pancreatic dysfunction, rather than insufficiency.

The nutritional status of patients with suspected or established PEI should be assessed with serial anthropometric parameters (body mass index, arm circumference, skinfold thickness). Functional parameters like grip strength or a 6 min walking test can help estimate the impact on performance status and functional reserve. If malnutrition is suspected, testing of serological parameters of malnutrition, such as plasma proteins, fat-soluble vitamins (A, D, E and K), magnesium, selenium and zinc, should be considered, though evidence for their diagnostic utility in PEI remains limited.

In certain circumstances when there is diagnostic uncertainty, assessing the clinical response (symptoms and nutritional improvement) to an empirical course of pancreatic enzyme replacement therapy (PERT) may be justified. Radiological tests are not recommended to diagnose PEI but can be valuable to determine underlying causes and should be considered after confirming PEI.

Direct invasive tests (duodenal fluid aspiration after intravenous administration of secretin or cholecystokinin) are no longer recommended to assess exocrine function. For assessing digestion, an indirect non-invasive test has been used historically, namely quantification of the coefficient of fat absorption after a 72-hour stool collection. However, it is expensive, logistically cumbersome to perform and not available routinely in hospital laboratories. The $^{13}$C-mixed triglyceride (13C-MTG) breath test is another test to assess fat absorption, but its use remains largely confined to research and is not routinely available in clinical practice. In addition, neither of these tests is specific to PEI and can yield positive results in patients with other causes of malabsorption. Therefore, in routine practice, faecal elastase (FE-1) remains the first-line test for PEI investigation.

#### The role of FE-1

FE-1 is the most common test used to diagnose PEI. It is widely available, easy to perform and inexpensive. It is a highly sensitive (94%) but only moderately specific (69%) test for PEI using the standard 200 µg/g cut-off. Classically, an FE-1 result of <200 µg/g stool suggests moderate PEI, while <100 µg/g suggests severe PEI. Levels between 200 and 500 µg/g are considered normal; however, their significance is unclear. A low FE-1 result should be considered with caution in scenarios with a low probability of PEI, as this increases the risk of a false positive result. A recent meta-analysis showed that lowering the cut-off to 100 µg/g improved specificity (0.82, 95% CI 0.58 to 0.94) with a slight reduction in sensitivity (0.88, 95% CI 0.78 to 0.94), providing flexibility in test interpretation based on clinical context.[3] Conversely, in patients with a high probability of PEI, the possibility of a false negative result should be considered when a normal FE-1 result is obtained. When requesting an FE-1, the patient should be educated on how to provide a stool sample, emphasising that watery or contaminated samples with urine may lead to a false positive result. Adjustment to standardised water content and repeating FE-1 in dubious cases are recommended.[4] In certain situations, the commencement of PERT without testing or waiting for FE-1 can be justified. These include pancreatic head cancer, necrotising pancreatitis, total pancreatectomy or pancreaticoduodenectomy, where the likelihood of PEI is high regardless of test results.

### Treatment

Patients with PEI should always be offered treatment with PERT, which has been shown to improve

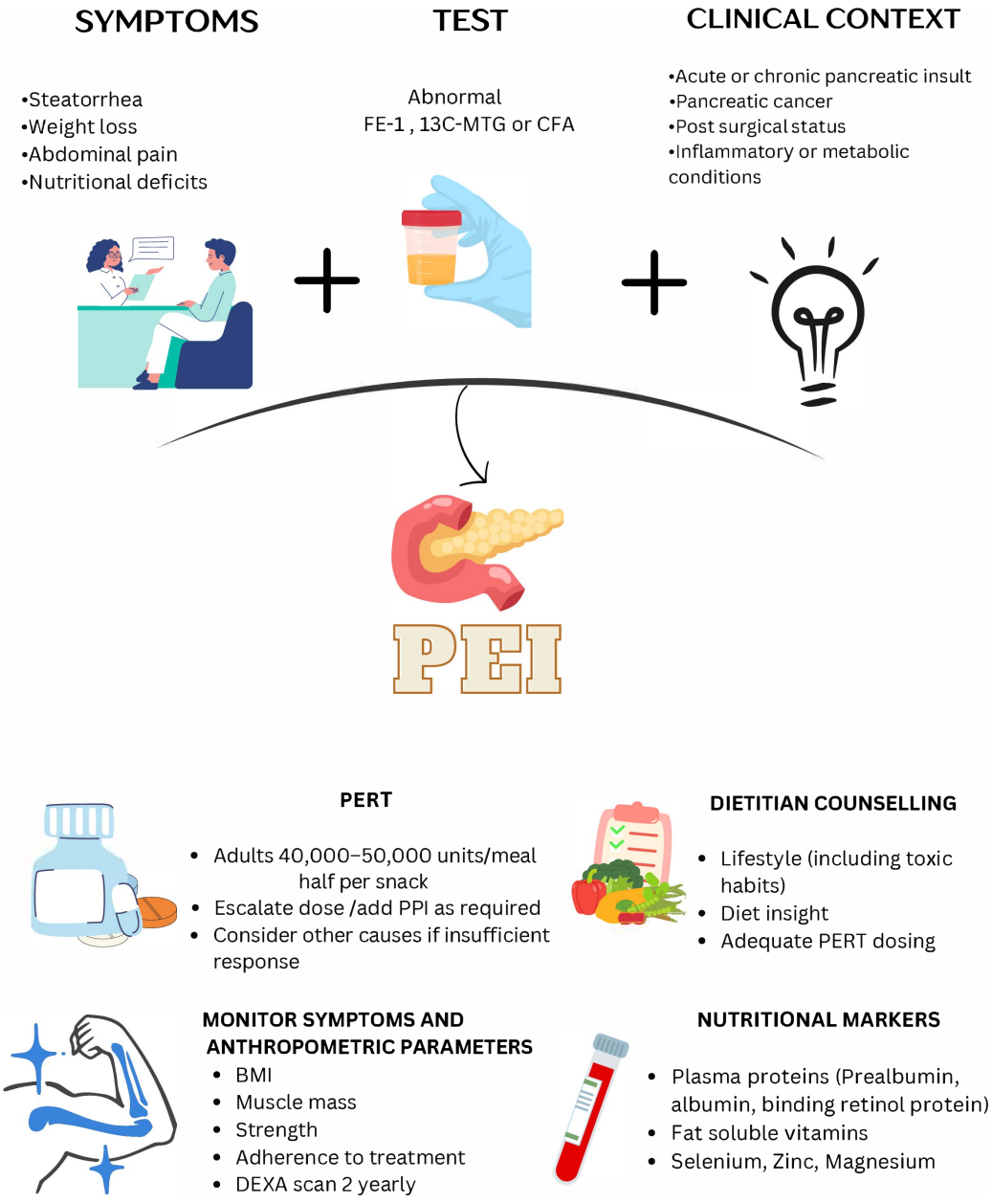


**Figure 1** Diagnosis and treatment of PEI. 13C-MTG, $^{13}$C-mixed triglyceride breath test; BMI, body mass index; CFA, coefficient of fat absorption; DEXA, dual X-ray absorptiometry; FE-1, faecal elastase; PEI, pancreatic exocrine insufficiency; PERT, pancreatic enzyme replacement therapy; PPI, proton pump inhibitor.

nutritional status, symptoms and quality of life.[5] The recommended initial dose is 40 000–50 000 units of lipase with main meals, and half of that dose (20 000–25 000 units) with snacks in adult patients. In children, 500–2500 lipase units/kg/meal or meal fat content (500-4000 units of lipase/g of fat/day) is used. In infants, 5000 lipase units per breastfeed or 100–120 mL of infant formula is advised. PERT should be taken around the time of the meal (either at the start, during or immediately after food), which allows them to mix with chyme to simulate the action of endogenous pancreatic enzymes. The regimen distribution should be adapted to each case to facilitate adherence. In special situations such as dysphagia, PERT can be suspended in acidic foods of puréed consistency. PERT can also be administered through feeding tubes every 2 hours or added directly to the formula.

Patients with PEI are advised to follow a healthy balanced diet with normal fat content. All patients with PEI should have access to experienced dietitians for nutritional care, who can educate them on the correct timing and dosing, perform dietary counselling and monitor adherence to treatment.

The response to treatment is defined as resolution of nutritional deficiencies and relief of symptoms. This should be ideally linked to improvement in serial anthropometric and functional parameters, biochemical

**Table 1** Estimated prevalence of PEI in different conditions

| Condition | Estimated PEI prevalence | Comments |
|---|---|---|
| Acute pancreatitis | ► 60% on admission<br>► 27–35% after the episode | ► Increases if recurring, severe and necrotising.<br>► Low threshold of starting PERT.<br>► On recovery, assess the need to continue PERT. |
| Chronic pancreatitis | ► 20–90% depending on the duration, severity and aetiology of the disease<br>► For example, 45% in AIP (IgG4-related disease) | PERT improves:<br>► Nutrition.<br>► QoL.<br>► Morbidity. |
| Cystic fibrosis | 75–90% | ► Any newly diagnosed CF or CFTR-RD should be tested for PEI, and if positive should be retested for confirmation in 3 months.<br>► Children who maintain pancreatic sufficiency should be tested annually with FE-1. |
| Pancreatic cancer | ► 70% for all forms<br>► >90% in HoP and in all forms of advanced disease | ► PERT improves nutritional status and QoL and may improve survival.<br>► PERT can be initiated after assessing symptoms and nutritional status, avoiding any pancreatic function test. |
| Pancreatic surgery | ► 90% in pancreatoduodenectomy<br>► 10–80% in body/tail (a reflection of the extent of surgery) | ► PERT can be initiated after assessing symptoms and nutritional status, avoiding any pancreatic function test.<br>► FE-1 not reliable. CFA or breath test preferred (if available). |
| Upper gastrointestinal surgery:<br>► Oesophageal<br>► Gastric<br>► Bariatric | 9–67%<br>► Based on the type of surgery | Intestinal asynchrony.<br>Altered neural and hormonal pathways.<br>FE-1 is not reliable in these scenarios.<br>► CFA or breath test preferred (if available). |
| Diabetes mellitus | 5–50% (pooled prevalence of 22%) | More common in type 1 than type 2.<br>Mechanisms include:<br>► Loss of the trophic effect of insulin.<br>► Autonomic dysfunction. |
| Ageing | 11–21% | Clinical significance uncertain. |
| Coeliac disease | 26.2% at diagnosis, dropping to 8% on a gluten-free diet | Linked to reversible mucosal atrophy. |
| IBD | Odds ratio of 10.5 compared with healthy controls | Higher prevalence of pancreatitis, for example, due to:<br>► Gallstones.<br>► Azathioprine-related pancreatitis.<br>► AIP (IgG4-related disease). |
| IBS-D | 4–13% | Whether PEI coexists or causes the symptoms remains unclear. |
| Drug-induced PEI | ► 1–10% in the use of immune-checkpoint inhibitors and tyrosine kinase inhibitors<br>► 8–24% in somatostatin analogues | ► ICI and TKI mechanism unclear.<br>► Somatostatin analogues suppress secretin, CCK and motilin. |
| CHF | 6.9–56.7% | Reduced splanchnic blood flow may affect pancreatic function in patients with CHF. |
| Infectious disease | 20–50% in HIV | No data on other infectious disease. |

AIP, autoimmune pancreatitis; CCK, cholecystokinin ; CF, cystic fibrosis; CFA, coefficient of fat absorption; CFTR-RD, cystic fibrosis transmembrane conductance regulator-related disorder; CHF, chronic heart failure; FE-1, faecal elastase; HoP, head of pancreas; IBD, inflammatory bowel disease; IBS-D, irritable bowel syndrome–diarrhoea predominant; ICI, immune-checkpoint inhibitors; IgG4, immunoglobulin G4; PEI, pancreatic exocrine insufficiency; PERT, pancreatic enzyme replacement therapy; QoL, quality of life; TKI, tyrosine kinase inhibitors.

markers and overall quality of life. Dose escalation and/or adding a proton pump inhibitor (PPI) should be provided on an individualised basis. Some guidelines suggest adding PPI prior to dose escalation if there is inadequate response,[4] along with further tests to rule out diseases such as small intestine bacterial overgrowth, microscopic colitis, inflammatory bowel disease, bile salt diarrhoea, infection, coeliac disease, lactase deficiency or other food intolerances that can mimic PEI. An incomplete or absent response should prompt checking adherence to treatment as well as considering whether the dose and manner of administration need to change. Equally, dietary fibre intake could be restricted if symptoms persist, especially in patients on a high-fibre diet.

## PEI in specific conditions

### Acute pancreatitis

The risk of PEI is estimated to be over 60% in acute pancreatitis (AP). PEI prevalence is higher in those with severe presentations, including severe necrotising pancreatitis cases. Given the low sensitivity of FE-1 for mild (0.47) or moderate (0.67) forms of PEI, a normal result may lead to under-reported prevalence.[6] PEI can improve or recover once acute inflammatory changes

have resolved, though reported prevalence remains 27–35%[7] after AP. Consequently, retesting for PEI at a 3-month interval after discharge is advised, with repeat testing at 6 and 12 months suggested in those who remain on PERT.

### Chronic pancreatitis

The prevalence of PEI in chronic pancreatitis (CP) is high and time dependent (with a reported range of 20–90%). Pathogenesis is explained by loss of pancreatic parenchyma replaced by fibrosis or obstruction of the pancreatic duct by inflammation or calculi. It is estimated that enzyme secretion must be reduced by 90% before developing steatorrhoea. This may explain the increased risk of PEI over time, with an estimated prevalence of 20% after 5 years and up to 70% after 20 years of pancreatic disease.[8] PERT improves quality of life and morbidity in these cases, although its impact on survival is less clear.

### Pancreatic cancer

PEI prevalence rate in pancreatic cancer (PC) is estimated to be around 70% (more than 80% in head of pancreas location or those in advanced stage).[9] As opposed to CP, pathogenesis seems to be more linked to the obstruction of the main pancreatic duct rather than replacement of pancreatic parenchyma by tumorous mass. PERT reduces weight loss and improves nutritional deficit and sarcopenia in patients with PC. There is mounting evidence that PERT may improve survival in this condition. Once PERT is started, patients should be regularly reassessed to ensure adequate response and offered enzyme dose escalation or treatment of nutritional deficits if appropriate.

Some conditions such as cystic fibrosis are known to have a strong link to PEI, but many other causes of PEI have been described, albeit based on lower evidence, such as case series and poor-quality case–control studies. These are summarised in table 1.

## SUMMARY

The new guidelines define PEI as a syndrome of maldigestion and malnutrition due to inadequate availability of pancreatic enzymes for digestion. Therefore, FE-1 alone is inadequate to reach a diagnosis, and cases need comprehensive assessment including the pretest probability and clinical manifestations. This new framework recommends assessment of PEI-related symptoms, nutritional status and pancreatic secretion, along with the pretest probability in certain clinical scenarios. FE-1 is convenient and accessible but limited by low specificity, sampling dilution and uncertainty about significance of 'indeterminate values' (generally defined as 200–500 $\mu$g/g). While the 13C-MTG breath test can also be recommended for the diagnosis of PEI, it is still unavailable in most clinical settings.

PERT reduces PEI-related morbidity and mortality. The optimal dose, the need for other formulations and more accurate assessments of patient response are areas where more robust evidence is required. When uncertainty arises, treatment with PERT can be justified with a positive response to treatment supporting the diagnosis of PEI. Reviewing the need for ongoing treatment with PERT in cases where pancreatic function may improve (such as acute pancreatitis or autoimmune pancreatitis) is recommended.

**Collaborators** Not applicable.

**Contributors** JMA and MJ drafted the manuscript. MSD, RM and BK were involved in critical revision and contribution to changes in its content. RM was involved in the review and drafted the key points of diagnosis and treatment. JMA was involved in table and figure creation. EW helped with the reviewers' comments and grammar.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Not commissioned; internally peer reviewed.



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