European Guideline on the diagnosis and therapy of pancreatic exocrine insufficiency

UEG, EPC, EDS, ESPGHAN and ESPCG evidence-based recommendations

Agenda

1. Welcome
2. Summary of progress made to date and updated timelines
3. Detailed voting results and revisions for Chapters 1-6
4. Next steps for the remaining chapters

European Guideline on the Diagnosis and Treatment of PEI

E·P·C
European Pancreatic Club
Founded 1965

Chapter	Coordinator(s)
1. Concept, Pathogenesis, and Clinical Relevance	J. Enrique Domínguez-Muñoz, Matthias Löhr
2. General Diagnostic Approach to PEI	Gabriele Capurso, Pali Hungin
3. General Therapeutic Approach to PEI	Peter Hegyi
4. PEI Secondary to Chronic Pancreatitis	Daniel de la Iglesia
5. PEI After Acute Pancreatitis	Vinciane Rebours, Johann Ockenga
6. PEI Associated with Pancreatic Cancer	Lukas Perkhofer, Natalya Gubergrits
7. PEI Secondary to Cystic Fibrosis	Isabelle Scheers
8. PEI After Pancreatic Surgery	Roberto Salvia
9. PEI After Oesophageal, Gastric, and Bariatric Surgery	Jonas Rosendahl
10. PEI in Patients with Type I and Type II Diabetes	Djuna Cahen
11. PEI in Other Conditions	Miroslav Vujasinovic

European Guideline on the Diagnosis and Treatment of PEI

- Agreement reached in chapters 1 to 6.

Achievement	Deadline
Delphi voting for chapters 7-8	3rd November
Delphi voting for chapters 9-11	24th November
Second rounds	15th December
Manuscript 1st draft	31st January
Manuscript submission	31st March
Official presentation	EPC meeting, June 2024

Chapter 1
Statements

1. PEI is defined as a reduction of pancreatic exocrine secretion and/or intraluminal activity of pancreatic enzymes below a level that permits normal digestion of nutrients. This is associated with malabsorption, and therefore, it may cause intestinal symptoms and/or nutritional deficiencies. (LE 5; SA 87.95%; A 8.43%; N 0%; D 2.41%; SD 1.2%)
2. The mechanisms leading to PEI are a reduced secretion of pancreatic enzymes and bicarbonate due to pancreatic disease and/or insufficient postprandial stimulation of the exocrine pancreas. (LE 1; SA 87.95%; A 9.64%; N 1.2%; D 1.2%; SD 0%)
3. PEI manifestations are influenced by several factors, including gastrointestinal anatomy, intraluminal pH, the compensatory activity of non-pancreatic digestive enzymes, intestinal function, dietary habits, and nutritional needs. (LE 3; SA 84.34%; A 13.25%; 2.41%; D 0%; SD 0%)
4. Intestinal symptoms and nutritional deficiencies are the main clinical manifestations and consequences of PEI. These consequences may have an impact on the quality of life and may put patients at risk of long-term malnutrition-related complications. (LE 1; SA 90.36%; A 7.23%; N 1.2%; D 1.2%; SD 0%)

Chapter 2
Statements

1. Diagnostic work-up should be done where there is an increased probability of PEI, such as in the presence of pre-existing conditions like cystic fibrosis, chronic pancreatitis, pancreatic cancer or surgery, as well as in patients with symptoms suggestive of malabsorption such as steatorrhea, chronic diarrhoea or in maldigestion. (LE 3; SA 86.57%; A 10.45%; N 1.49%; D 1.49%; SD 1.2%)
2. As a rule, diagnosis of PEI should be based on the combined evaluation of symptoms, nutritional status and pancreatic function in the appropriate clinical context. (LE 3; SA 88.0%; A 9.33%; N 1.33%; D 1.33%; SD 0%)
3. In patients with pancreatic disease or previous pancreatic surgery, the presence of symptoms of maldigestion supports the diagnosis of PEI. The presence of clinically evident steatorrhoea might be sufficient to make a diagnosis of PEI in these patients, especially if no other cause of symptoms is suspected, but additional nutritional evaluation and pancreatic function testing are recommended.(LE 3; SA 84.0%; A 10.67%; N 1.33%; D 4.0%; SD 0%)
4. Nutritional markers, including fat soluble vitamins, proteins and trace elements, are frequently abnormal in patients with PEI and can be used, together with the evaluation of pancreatic function and maldigestion-related symptoms, to support the diagnosis of PEI in patients with pancreatic disease or surgery. (LE 3; SA 91.04%; A 5.97%; N 2.99%; D 0%; SD 0%)

Chapter 2
Statements

5. The nutritional status of patients with PEI is primarily assessed by clinical parameters, including body weight / BMI and weight loss. In case of clinical suspicion of malnutrition, lean body mass and potential sarcopenia could also be assessed and established blood parameters of malnutrition such as prealbumin, retinol-binding protein, transferrin, fat-soluble vitamins, and minerals/trace elements (including serum zinc and magnesium) should be measured. (LE 3; SA 80.6%; A 14.93%; N 4.48%; D 0%; SD 0%)
6. The pancreatic exocrine function can be evaluated by means of direct, invasive tests, measuring the content of the pancreatic fluid in the duodenum after stimulation, non-invasive tests that quantify pancreatic enzymes in faeces, or indirect, non-invasive tests evaluating the effects of the lack of pancreatic enzymes on digestion. (LE 5; SA 89.55%; A 8.96%; N 0%; D 0%; SD 1.49%)
7. Invasive, direct pancreatic function test are not recommended for the diagnosis of PEI in clinical routine. (LE 3; SA 100%; A 0%; N 0%; D 0%; SD 0%)
8. In clinical practice, non-invasive tests such as faecal elastase and 13C-mixed triglyceride breath test are recommended to assess pancreatic exocrine function with good accuracy, the latter being also useful for monitoring of pancreatic enzyme replacement therapy. (LE 2; SA 91.04%; A 7.46%; N 0%; D 1.49%; SD 0%)

Chapter 2
Statements

9. In patients with a very high probability of PEI, such as those with pancreatic cancer located in the head of the pancreas, and those after pancreaticoduodenectomy or total pancreatectomy, confirmation of PEI by pancreatic function tests is not always required. (LE 2; SA 86.67%; A 10.67%; N 1.33%; D 1.33%; SD 0%)
10. Radiological imaging is not recommended to diagnose Pancreatic exocrine insufficiency (PEI). (LE 4; SA 89.55%; A 8.96%; N 1.49%; D 0%; SD 0%)
11. If the diagnosis of PEI cannot be established after evaluation of symptoms, nutritional status and pancreatic function, evaluation of the clinical response to empirical PERT could be of help in the appropriate clinical context. (LE 5; SA 84.0%; A 13.33%; N 0%; D 2.67%; SD 0%)

Chapter 3
Statements

1. Pancreatic exocrine insufficiency should be treated with PERT. (LE 1; SA 95.12%; A 3.66%; N 0%; D 1.22%; SD 0%)
2. The use of PERT should be considered in chronic pancreatitis (CP), following acute pancreatitis (AP), in pancreatic cancer (PC), cystic fibrosis (CF) following pancreatic surgery and could be evaluated in other metabolic or gastroenterological conditions. (LE 3; SA 80.49%; A 9.76%; N 2.44%; D 7.32%; SD 0%)
3. Pancreatic enzyme preparations (pancreatin) are the first-line treatment of PEI. (LE 1; SA 96.39%; A 2.41%; N 0%; D 0%; SD 1.2%)
4. Enteric-coated microspheres or mini-microspheres are the preparations of choice for PEI. (LE 2; SA 92.77%; A 6.02%; N 1.2%; D 0%; SD 0%)
5. The most frequently used PERT preparations are of porcine origin. Patients should be made aware of the porcine origin of PERT before commencing therapy. (LE 5; SA 80.72%; A 14.46%; N 4.82%; D 0%; SD 0%)
6. Initial doses of PERT are variable depending on the age of the patient (adulthood or childhood), and on the severity of PEI. (LE 3; SA 87.95%; A 6.02%; N 4.82%; D 1.2%; SD 0%)
7. If PERT is prescribed for PEI, the capsules should be taken along with the meals and snacks. (LE 2; SA 91.46%; A 3.66%; N 3.66%; D 1.22%; SD 0%)

Chapter 3
Statements

8. Successful PERT can be defined as the resolution of malnutrition, symptoms and signs associated with pancreatic exocrine insufficiency in an individual patient. (LE 5; SA 87.95%; A 9.64%; N 1.2%; D 1.2%; SD 0%)

9. A proportion of patients with PEI may not achieve complete treatment success with PERT, even after optimization of therapy (compare Q6). However, also partial success can justify the continuation of PERT. It is achieved if part of the symptoms/signs are resolved or improved in a clinically meaningful way. (LE 5; SA 86.75%; A 10.84%; N 0%; D 1.2%; SD 1.2%)

10. Non-responders or partial responders to PERT should be evaluated to detect problems in adherence, errors in the administration of PERT, and signs and symptoms of other diseases. Dose escalation and/or PPI treatment, as well as tests to rule out other diseases, should be implemented in a personalized manner. (LE 4; SA 93.98%; A 4.82%; N 0%; D 1.2%; SD 0%)

11. Restriction of dietary fibre in patients taking very high-fibre diets may be required where PEI symptoms persist despite apparently adequate PERT. (LE 4; SA 79.52%; A 7.23%; N 13.25%; D 0%; SD 0%)

12. Patients with PEI should have access to an experienced dietitian to manage their nutritional care. (LE 4; SA 83.13%; A 10.84%; N 3.61%; D 2.41%; SD 0%)

Chapter 3
Statements

13. In patients receiving enteral feeding, if there is intolerance to standard polymeric feeds, peptide- and medium-chain triglyceride (MCT)-based formulae could be tried. (LE 5; SA 79.52%; A 12.05%; N 6.02%; D 1.2%; SD 1.2%)
14. PERT improves fat and protein absorption in patients with PEI. (LE 1; SA 89.16%; A 7.23%; N 2.41%; D 0%; SD 1.2%)
15. PERT has a beneficial effect on body weight, nutritional status, symptoms and quality of life in patients with PEI. (LE 1; SA 91.57%; A 7.23%; N 0%; D 0%; SD 1.2%)
16. PERT might have a beneficial effect in morbidity and mortality in patients with PEI. (LE 5; SA 78.31%; A 12.05%; N 6.02%; D 3.61%; SD 0%)
17. PERT is not associated with major adverse effects, and most reported symptoms are consistent with the underlying disease.. (LE 1; SA 92.77%; A 7.23%; N 0%; D 0%; SD 0%)
18. There is no evidence to suggest any detrimental effects are associated with the use of PERT in pregnancy or lactation. (LE 4; SA 92.77%; A 4.82%; N 2.41%; D 0%; SD 0%)
19. PERT could be added to enteral nutrition if required but there is no data on the clinical efficacy of this technique. (LE 4; SA 89.16%; A 4.82%; N 3.61%; D 2.41%; SD 0%)
20. PERT products should be suspended in an appropriate food stuff in patients with dysphagia. (LE 5; SA 83.13%; A 12.05%; N 2.41%; D 2.41%; SD 0%)

Chapter 4
Statements

1. The prevalence of PEI in chronic pancreatitis ranges from 20% to 90% depending on disease duration, severity, and aetiology (LE 4, SA 89.5%; A 8.9%; N 0%; D 1.5%; SD 0%)
2. Based on clinical criteria and/or non-invasive tests, the reported pooled prevalence of PEI in patients with autoimmune pancreatitis is approximately 45% (LE 3, SA 82.3%; A 8.1%; N 6.4%; D 3.2%; SD 0%
3. PEI in CP results from loss of functioning pancreatic parenchyma and/or obstruction of the pancreatic duct (LE 1; SA 92.4%; A 6.1%; N 0%; D 1.5%; SD 0%)
4. The diagnosis of PEI in patients with CP follows the general recommendation (see Chapter 2) (LE 1; SA 95.6%; A 4.4%; N 0%; D 0%; SD 0%)
5. Clinical consequences of PEI in chronic pancreatitis are comparable to other etiologies. (see question 1.4.) (LE 1; SA 92.6%; A 5.8%; N 0%; D 1.4%; SD 0%)
6. PEI treatment in CP follows general recommendations (Chapter 3) (LE 1; SA 95.5%; A 4.5%; N 0%; D 0%; SD 0%)
7. PERT improves digestion and nutrient absorption in patients with PEI secondary to CP (Grade 1A; SA 92.4%; A 7.6%; N 0%; D 0%; SD 0%)

Chapter 4
Statements

8. PERT improves the quality of life in patients with PEI secondary to CP (LE 4; SA 90.9%; A 7.6%; N 1.52%; D 1.2%; SD 0%)
9. It is unclear to what extent PERT can reduce mortality but can reduce probably long-term morbidity in patients with PEI secondary to CP (LE 3; SA 87.7%; A 6.2%; N 1.5%; D 3.1%; SD 1.5%)
10. PERT adverse events in CP are similar to those in other conditions (Chapter 3) (Grade 1B; SA 93.9%; A 6.1%; N 0%; D 0%; SD 0%)
11. In patients with PEI secondary to CP, a structured assessment including clinical symptoms, nutritional status, and biochemical parameters (see Table X) is suggested. The frequency of assessment is variable depending on the patient's clinical situation and the severity of the disease (LE 7; SA 75.7%; A 15.2%; N 6.1%; D 3.0%; SD 0%)

Chapter 5
Statements

1. Pooled reported prevalence of PEI after acute pancreatitis (AP) is of 27% to 35%. PEI is more prevalent in severe forms of AP and patients with extensive pancreatic necrosis, as well as after AP in patients with alcohol abuse (LE 4; SA 85.7%; A 12.7%; N 1.6%; D 0%; SD 0%)
2. The pathogenesis of PEI in patients with acute pancreatitis is incompletely understood but loss of pancreatic acinar tissue due to necrosis, and ductal stenosis or leakage may be associated with this complication (LE 5 ; SA 87.5%; A 9.4%; N 1.6%; D 0%; SD 1.6%)
3. The diagnosis of PEI in patients after AP follows the general recommendation (Chapter 2) (SA 96.9%; A 3.1%; N 0%; D 0%; SD 0%)
4. All patients should be screened for PEI after an episode of acute pancreatitis, mainly those after severe disease, pancreatic necrosis, or alcoholic aetiology. Although previously normal, screening for PEI should be repeated when symptoms attributable to PEI occur (LE 5; SA 79.4%; A 9.5%; N 1.6%; D 7.9%; SD 1.6%)
5. No delay is recommended to confirm the diagnosis of PEI after the recovery of acute pancreatitis. Pancreatic function may recover after AP and therefore PEI may be temporary in some patients (LE 5; SA 85.2%; A 6.6%; N 3.3%; D 3.3%; SD 1.6%)
6. Empirical treatment can be considered in the presence of symptoms of maldigestion or nutritional deficiencies, mainly after severe necrotizing pancreatitis. A clear response would be both diagnostic and therapeutic for PEI (LE 5; SA 80.9%; A 14.3%; N 3.1%; D 1.6%; SD 0%)

Chapter 5
Statements

7. Clinical consequences of PEI after AP are comparable to other PEI etiologies. (SA 89.1%; A 7.8%; N 0%; D 3.1%; SD 0%)
8. It is possible that PEI could have an influence on functional recovery, length of hospitalization and quality of life in the early course after AP (Grade 2B; SA 82.8%; A 9.4%; N 3.1%; D 4.7%; SD 0%)
9. PEI treatment after AP follows the general recommendation (Chapter 3) (SA 93.9%; A 4.5%; N 0%; D 1.5%; SD 0%)
10. PERT could be added to enteral nutrition in patients with severe necrotising AP, but data on efficacy and feasibility are scarce (LE 4; SA 85%; A 8.3%; N 1.7%; D 3.3%; SD 1.7%)
11. PERT is likely to relieve symptoms of maldigestion and avoid nutritional deficiencies in patients with PEI after AP, but specific data are lacking. There is insufficient evidence about the benefit of PERT for PEI during admission of AP (LE 5; SA 88.9%; A 4.8%; N 1.6%; D 3.2%; SD 1.6%)
12. In patients with PEI secondary to acute pancreatitis, and as a general recommendation, clinical symptoms, nutritional status, a non-invasive test for PEI (e.g., faecal elastase) and compliance to PERT can be monitored at 3, 6 and 12 months after hospital discharge, and then every 6 to 12 months in case of persistent PEI (LE 5; SA 80.7%; A 12.9%; N 1.6%; D 3.2%; SD 1.6%)

Chapter 6
Statements

1. PEI develops in approximately 70% of patients with PC. PEI is more frequent in patients with the tumour located at the head of the pancreas and in patients with advanced stages of the disease (LE 1; SA 93.4%; A 6.6%; N 0%; D 0%; SD 0%)
2. The prevalence of PEI in patients with advanced pancreatic cancer increases during the course of the disease (LE 4; SA 93.3%; A 5%; N 1.7%; D 0%; SD 0%)
3. PEI in pancreatic cancer is mainly caused by tumour obstruction of the main pancreatic duct. Atrophy, replacement of the pancreatic parenchyma and loss of pancreatic exocrine tissue may also play a role (LE 1; SA 90.2%; A 3.3%; N 1.6%; D 3.3%; SD 1.6%)
4. Diagnosis of PEI in PC follows the general recommendation (Chapter 2).(SA 92.2%; A 4.7%; N 0%; D 3.1%; SD 0%)
5. PEI contributes to malnutrition and weight loss in pancreatic cancer patients (LE 3; SA 95%; A 5%; N 0%; D 0%; SD 0%)
6. PEI increases the risk of sarcopenia in patients with pancreatic cancer (LE 3; SA 90%; A 6.7%; N 3.3%; D 0%; SD 0%)

Chapter 6
Statements

7. The severity of PEI based on the FE-1 test correlates with the survival of patients with advanced pancreatic cancer (LE 3; SA 82.7%; A 6.9%; N 6.9%; D 3.5%; SD 0%)
8. Untreated PEI harms quality-of-life in patients with pancreatic cancer (LE 4; SA 90.2%; A 3.3%; N 4.9%; D 1.6%; SD 0%)
9. Treatment of PEI in PC follows the general recommendation (Chapter 3)(SA 88.9%; A 4.7%; N 4.7%; D 1.6%; SD 0%)
10. PERT improves PEI-related symptoms in pancreatic cancer patients (LE 3; SA 91.8%; A 8.2%; N 0%; D 0%; SD 0%)
11. PERT can improve the nutritional status of pancreatic cancer patients (LE 1; SA 90.2%; A 8.2%; N 1.6%; D 0%; SD 0%)
12. PERT may positively affect overall survival in pancreatic cancer patients with PEI (LE 2; SA 85%; A 6.7%; N 6.7%; D 0%; SD 1.6%)
13. Pancreatic cancer patients with PEI should be monitored regularly to ensure they receive sufficient management advice and control their symptoms. Regular review should be undertaken to ensure they do not require dose escalation or treatment of associated conditions such as anaemia and other micronutrient deficiency (LE 4; SA 88.3%; A 6.7%; N 1.6%; D 3.3%; SD 0%)