Pancreatology 25 (2025) 293–300

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Recommendations from the European guidelines for the diagnosis and therapy of pancreatic exocrine insufficiency

Miroslav Vujasinovic [a, b, *, 1], Daniel de la Iglesia [c, 1], J. Enrique Dominguez-Muñoz [d, 2], J. Matthias Löhr [a, e, 2], on behalf of the European PEI Multidisciplinary Group[3]

[a] Department of Upper Abdominal Diseases, Karolinska University Hospital, Stockholm, Sweden
[b] Department of Medicine Huddinge, Karolinska Institute, Stockholm, Sweden
[c] Department of Gastroenterology, University Hospital Puerta de Hierro, Madrid, Spain
[d] Department of Gastroenterology and Hepatology, University Hospital of Santiago de Compostela, Santiago de Compostela, Spain
[e] Department of Clinical Sciences, Karolinska Institute and Department of Upper Abdominal Diseases, Karolinska University Hospital, Stockholm, Sweden

ARTICLE INFO

Article history:
Received 21 December 2024
Received in revised form
17 February 2025
Accepted 27 February 2025
Available online 28 February 2025

Keywords:
Pancreatic
Exocrine
Insufficiency
Guideline
PERT

ABSTRACT

Background: Pancreatic exocrine insufficiency (PEI) is defined as a reduction in pancreatic exocrine secretion below a level that allows normal digestion of nutrients. Pancreatic disease and pancreatic surgery are the main causes of PEI, but other conditions can affect the digestive function of the pancreas.
Methods: In collaboration with European Digestive Surgery (EDS), European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), European Society for Clinical Nutrition and Metabolism (ESPEN), European Society of Digestive Oncology (ESDO), and European Society of Primary Care Gastroenterology (ESPCG) the working group developed European guidelines for the diagnosis and therapy of PEI. United European Gastroenterology (UEG) provided both endorsement and financial support for the development of the guidelines.
Results: Recommendations covered topics related to the clinical management of PEI: concept, pathogenesis, clinical relevance, general diagnostic approach, general therapeutic approach, PEI secondary to chronic pancreatitis, PEI after acute pancreatitis, PEI associated with pancreatic cancer, PEI secondary to cystic fibrosis, PEI after pancreatic surgery, PEI after esophageal, gastric, and bariatric surgery, PEI in patients with type 1 and type 2 diabetes, and PEI in other conditions.
Conclusions: The European guidelines for the diagnosis and therapy of PEI provide evidence-based recommendations concerning key aspects of the etiology, diagnosis, therapy, and follow-up, based on current available evidence. These recommendations should serve as a reference standard for existing management of PEI and as a guide for future clinical research. This article summarizes the recommendations and statements.

1. Introduction

Pancreatic exocrine insufficiency (PEI) has long been thought to be solely the result of a secretory deficiency, either of enzymes and/or bicarbonate secretion from the pancreas [1]. As a result, PEI has been seen almost exclusively in the context of pancreatic disease, primarily chronic pancreatitis (CP) and cystic fibrosis (CF), and later pancreatic cancer or after pancreatic resection. Accordingly, guidelines dealing with PEI have focused almost exclusively on these four conditions.

Regarding PEI, two interrelated issues have emerged: firstly, PEI must be viewed as a maldigestive syndrome rather than an isolated

Abbreviations: AP, acute pancreatitis; CF, cystic fibrosis; CP, chronic pancreatitis; FE-1, fecal elastase-1; GI, gastrointestinal; GRADE, grading of recommendations assessment, development, and evaluation; PEI, pancreatic exocrine insufficiency; PERT, pancreatic enzyme replacement therapy.

* Corresponding author. Department of Upper Abdominal Diseases, Karolinska University Hospital, 141 86, Stockholm, Sweden.
E-mail address: miroslav.vujasinovic@regionstockholm.se (M. Vujasinovic).

[1] Authors contributed equally and share the first authorship.
[2] Authors contributed equally and share the last authorship.
[3] The following colleagues contributed as working group members and, as members of the European PEI Multidisciplinary Group.

https://doi.org/10.1016/j.pan.2025.02.015
1424-3903/

organ defect. This means that the diagnosis and treatment of PEI must extend beyond the pancreas. Secondly, defining PEI not only as a lack of secreting enzymes, but as a lack of pancreatic digestion leading to malnutrition, requires a more holistic view of PEI. This has led to a new definition of PEI: a reduction in exocrine pancreatic secretion and/or intraluminal activity of pancreatic enzymes below a level that allows normal digestion of nutrients [2]. This is associated with malabsorption of nutrients and therefore intestinal symptoms and/or nutritional deficiencies.

2. Methods

On behalf of the European Pancreatic Club (EPC), four EPC members (lead, co-chair, and scientific secretaries) constitute the steering committee responsible for the design of the guideline protocol. The working group received endorsements and funding from United European Gastroenterology (UEG). The EPC invited other UEG Specialist Member Societies to join this project with the aim of developing multidisciplinary guidelines to be adopted by all specialties around Europe: European Digestive Surgery (EDS), European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), European Society for Clinical Nutrition and Metabolism (ESPEN), European Society of Digestive Oncology (ESDO), and European Society of Primary Care Gastroenterology (ESPCG).

Statements were formulated in the context of PICO questions [3] where applicable. The quality of evidence was appraised according to the Oxford Centre for Evidence-Based Medicine (OCEBM) system (grading was based on evidence levels 1 to 5, where level 1 is the highest and 5 is the lowest) [4,5]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [6] was solely used for appraising evidence based on controlled clinical trials. All questions with statements and comments were then subjected to a repeated Delphi process for all participants in the Guidelines Consortium. A level of agreement of 80 % or higher was considered indicative of consensus. Those statements with less than 80 % agreement were subjected to live discussion and TED voting as described [7,8].

We aim to publish these guidelines in Pancreatology to reach a broader and more diverse audience within the pancreatology community. By doing so, we hope to foster greater collaboration and ensure that these important guidelines are accessible to healthcare professionals working in various aspects of pancreatic disease management worldwide. This version represents a more concise summary of the original manuscript published in UEGJ, maintaining key insights while making the guidelines more accessible.

3. Results

3.1. Concept, pathogenesis, and clinical relevance of PEI

- PEI is defined as a reduction in exocrine pancreatic secretion and/or intraluminal activity of pancreatic enzymes below a level that allows normal digestion of nutrients. PEI is associated with malabsorption of nutrients and may result in intestinal symptoms and/or nutritional deficiencies [2].
  Consensus; Percentage of agreement: 97.4 %
- The mechanisms leading to PEI are reduced secretion of pancreatic enzymes and bicarbonate due to pancreatic disease or insufficient postprandial stimulation of the exocrine pancreas [2].
  Level of evidence: 1. Percentage of agreement: 97.6 %
- Whatever the cause of PEI, intestinal symptoms and nutritional deficiencies are the main clinical manifestations and consequences of PEI. These consequences can affect quality of life and put patients at risk of long-term malnutrition-related complications [2].
  Level of evidence: 1. Percentage of agreement: 97.6 %

3.2. General diagnostic approach to PEI

- In general, the diagnosis of PEI should be based on the combined assessment of symptoms, nutritional status and pancreatic function in the appropriate clinical context [2].
  Level of evidence: 3. Percentage of agreement: 97.3 %
- Confirmation of PEI may not always require pancreatic function tests in patients with a high likelihood of PEI, such as those with pancreatic cancer located in the head of the pancreas or those who have undergone pancreaticoduodenectomy or total pancreatectomy [2].
  Level of evidence: 2. Percentage of agreement: 97.3 %
- In patients with pancreatic disease or previous pancreatic surgery, the diagnosis of PEI is supported by the presence of symptoms of malabsorption. However, symptoms are neither sensitive nor specific to PEI and additional nutritional evaluation and pancreatic function testing may be used [2].
  Level of evidence: 3. Percentage of agreement: 94.7 %
- Patients with PEI often have nutritional deficiencies, and nutritional assessment can aid in the diagnosis of PEI in patients with pancreatic disease or surgery [2].
  Level of evidence: 3. Percentage of agreement: 97.0 %
- The nutritional status of patients with PEI is evaluated primarily using anthropometric parameters. If malnutrition is suspected, blood parameters of malnutrition should be assessed [2].
  Level of evidence: 3. Percentage of agreement: 95.5 %
- Pancreatic secretion can be evaluated through direct invasive tests which measure the stimulated pancreatic secretion in duodenal fluid, or non-invasive tests that quantify pancreatic enzymes in faeces. Indirect non-invasive tests can be used to evaluate the effect of the lack of pancreatic enzymes on digestion [2].
  Level of evidence: 3. Percentage of agreement: 98.5 %
- Direct pancreatic function tests should not be used for the diagnosis of PEI in clinical practice [2].
  Level of evidence: 3. Percentage of agreement: 100 %
- Non-invasive tests such as fecal elastase (FE-1) and the ^{13}C-mixed triglyceride breath test are recommended for assessing pancreatic exocrine function in clinical practice [2].
  Level of evidence: 2. Percentage of agreement: 98.5 %
- PEI cannot be diagnosed using radiological imaging [2].
  Level of evidence: 4. Percentage of agreement: 98.5 %
- If a diagnosis of PEI cannot be established based on the combined evaluation of symptoms, nutritional status, and pancreatic function, assessment of the clinical response to empirical pancreatic enzyme replacement therapy (PERT) may be useful in the appropriate clinical context [2].
  Level of evidence: 5. Percentage of agreement: 97.3 %

3.3. General therapeutic approach to PEI

- Pancreatic exocrine insufficiency should always be treated [2].
  Level of evidence: 1. Percentage of agreement: 98.8 %
- The use of PERT is indicated in patients with PEI secondary to CP after acute pancreatitis (AP), pancreatic cancer, CF, pancreatic surgery and possibly other metabolic or gastroenterological conditions [2].
  Level of evidence: 1. Percentage of agreement: 90.3 %

- PERT positively affects body weight, nutritional status, symptoms, and quality of life in patients with PEI [2].
  Level of evidence: 1. Percentage of agreement: 98.8 %
- PERT may reduce morbidity and mortality in patients with PEI [2].
  Level of evidence: 3. Percentage of agreement: 90.4 %
- Pancreatic enzyme preparations, specifically pancreatin, are the recommended first-line treatment for PEI [2].
  Level of evidence: 1. Percentage of agreement: 98.8 %
- Enteric-coated pellets of small size are the preferred pancreatin preparations for PEI [2].
  Level of evidence: 2. Percentage of agreement: 98.8 %
- The most used PERT preparations are of porcine origin. Patients should be informed of the porcine origin of PERT before therapy is initiated [2].
  Level of evidence: 5. Percentage of agreement: 95.2 %
- The initial doses of PERT vary mainly depending on the patient's age (adult or child), the severity of PEI, and the fat content of the meal. The administration of a minimum dose of 40,000–50,000 units of lipase with main meals and half of that dose (20,000–25,000 units) with snacks has been shown to be effective in adult patients [9,10]. A higher starting dose of PERT has been reported as effective in patients with more severe PEI, such as after pancreaticoduodenectomy [2].
  Level of evidence: 3. Percentage of agreement: 94.0 %
- PERT preparations should be taken with meals and snacks [2].
  Level of evidence: 2. Percentage of agreement: 95.1 %
- Successful PERT can be defined as the resolution of nutritional deficiencies and relief of symptoms and signs associated with PEI [2].
  Level of evidence: 5. Percentage of agreement: 97.6 %
- Patients who do not respond or only partially respond to PERT should be evaluated for adherence problems and inadequate administration of PERT. Enzyme dose escalation and/or additional treatment with a proton pump inhibitor should be applied on an individualized basis, along with testing to rule out other diseases [2].
  Level of evidence: 4. Percentage of agreement: 98.8 %
- In patients with dysphagia, PERT products should be suspended in an acidic food with puree consistency [2].
  Level of evidence: 5. Percentage of agreement: 95.2 %

3.4. PEI secondary to chronic pancreatitis

- The prevalence of PEI in chronic pancreatitis (CP) ranges from 20 % to 90 % depending on the duration, severity, and etiology of the disease [2].
  Level of evidence 4. Percentage of agreement: 98.5 %
- Based on clinical criteria and/or non-invasive tests, the reported pooled prevalence of PEI in patients with autoimmune pancreatitis (AIP) is approximately 45 % [2].
  Level of evidence: 3. Percentage of agreement: 90.5 %
- PEI in CP results from loss of functioning pancreatic parenchyma and/or obstruction of the pancreatic duct [2].
  Level of evidence: 1. Percentage of agreement: 98.5 %

3.5. PEI after acute pancreatitis (AP)

- The pooled reported prevalence of PEI after AP is 27 %–35 %. PEI is more common in severe forms of AP and in patients with extensive pancreatic necrosis, and after AP in patients with alcohol abuse [2].
  Level of evidence: 4. Percentage of agreement: 98.4 %
- All patients should be screened for PEI after an episode of AP, especially those with severe disease, pancreatic necrosis, or alcoholic etiology. Although previously normal, screening for PEI should be repeated if symptoms attributable to PEI develop [2].
  Level of evidence: 5. Percentage of agreement: 87.5 %
- Empirical treatment may be considered in the presence of symptoms of maldigestion or nutritional deficiencies, especially after severe necrotizing pancreatitis. A clear response would be both diagnostic and therapeutic for PEI [2].
  Level of evidence: 5. Percentage of agreement: 95.3 %

3.6. PEI associated with pancreatic cancer

- PEI occurs in around 70 % of patients with pancreatic cancer. It is more common in patients with tumors located in the head of the pancreas and in those with advanced stages of the disease [2].
  Level of evidence: 1. Percentage of agreement: 100 %
- The prevalence of PEI in patients with advanced pancreatic cancer increases as the disease progresses [2].
  Level of evidence: 4. Percentage of agreement: 98.4 %
- PEI increases the risk of sarcopenia in pancreatic cancer patients, which is associated with a poor prognosis [2].
  Level of evidence: 3. Percentage of agreement: 96.7 %
- Untreated PEI affects quality of life in pancreatic cancer patients [2].
  Level of evidence: 4. Percentage of agreement: 93.6 %
- PERT improves PEI-related symptoms in pancreatic cancer patients [2].
  Level of evidence: 3. Percentage of agreement: 100 %
- PERT can improve the nutritional status of pancreatic cancer patients [2].
  Level of evidence: 1. Percentage of agreement: 98.4 %

3.7. PEI in cystic fibrosis (CF) and CFTR-related disorders (CFTR-RD)

- PEI occurs in 75–90 % of patients with cystic fibrosis [2].
  Level of evidence: 1. Percentage of agreement: 96.5 %
- In patients with CF, confirmation of PEI is required as soon as CF is diagnosed. A positive test should be confirmed by a second test within three months. Subjects with clearly established PEI need no further PEI testing. Subjects with an equivocal exocrine function test should be monitored in the same way as pancreatic sufficient subjects [2].
  Level of evidence: 4. Percentage of agreement: 92.5 %
- Children with pancreatic sufficiency should be monitored with annual FE-1 or additionally in cases of failure to thrive, weight loss, abdominal pain or diarrhea [2].
  Level of evidence: 4. Percentage of agreement: 92.5 %
- In pancreatic sufficient adults surveillance for development of PEI can be individualized according to genotype [2].
  - Pancreatic sufficient subjects with a combination of two class I–III mutations known to be associated with intermediate to high prevalence of PEI could be evaluated with FE-1 testing annually and additionally if the development of PEI is suspected.
  - Subjects with one or more class IV-VI mutations known to be associated with low prevalence of PEI could be evaluated upon suspected development of PEI.

  Level of evidence: 4. Percentage of agreement: 92.5 %
- In patients with CFTR-RD, evaluation of PEI is required as part of the workup for CFTR-RD at any age. A positive test should be confirmed with a second test within three months [2].

Level of evidence: 5. Percentage of agreement: 92.5 %

- Pancreatic sufficient patients with CFTR-RD should be monitored by annual FE-1 during infancy and childhood or additionally in case of failure to thrive, weight loss, deficiencies in fat soluble vitamins, episodes of acute pancreatitis or diarrhea [2].
  Level of evidence: 4. Percentage of agreement: 92.5 %

3.8. PEI after pancreatic surgery

- The prevalence of PEI after pancreatic surgery is highly variable, ranging from 100 % after total pancreatectomy to 10 % in some reports after distal or central pancreatectomy [2].
  Level of evidence: 1. Percentage of agreement: 98.3 %
- The diagnosis of PEI in patients after pancreatic surgery mainly follows the general rules described previously with two exceptions: firstly, no diagnostic confirmation is required after total pancreatectomy; and secondly, the fecal elastase test is not suitable for the diagnosis of PEI after pancreaticoduodenectomy [2].
  Level of evidence: 1. Percentage of agreement: 84.2 %
- Treatment of PEI after pancreatic surgery follows the general rules described previously. However, the initial oral dose of pancreatic enzymes required in patients after total pancreatectomy and pancreaticoduodenectomy may be higher than that generally recommended for PEI secondary to other conditions [2].
  Level of evidence: 4. Percentage of agreement: 91.7 %

3.9. PEI after upper gastrointestinal (esophageal, gastric, bariatric) surgery

- The prevalence of PEI after upper gastrointestinal (GI) surgery ranges from 9 % to 67 %, depending on the type of surgery and the test used to diagnose PEI [2].
  Level of evidence: 3. Percentage of agreement: 96.9 %
- PEI after upper GI surgery may be the result of impaired stimulation of digestive enzyme secretion (humoral and neural) and postprandial GI asynchrony [2].
  Level of evidence: 5. Percentage of agreement: 98.4 %
- Fecal elastase-1 is not a reliable test for PEI after upper GI surgery [2].
  Level of evidence: 5. Percentage of agreement: 83.6 %
- The 13C-mixed triglyceride breath test and the quantification of the coefficient of fat absorption (CFA) could be used to diagnose PEI after upper GI surgery [2].
  Level of evidence: 5. Percentage of agreement: 91.8 %

3.10. PEI and diabetes mellitus

- Reduced pancreatic secretion, as assessed by fecal elastase-1, is a common condition in patients with type 1 and type 2 DM. The prevalence of PEI according to the agreed definition in presenting guidelines is unknown [2].
  Level of evidence: 3. Percentage of agreement: 94.2 %
- Proposed mechanisms of PEI in DM include the loss of the trophic and stimulatory effects of insulin on the exocrine pancreas [11], pancreatic atrophy, autonomic dysfunction [11,12], fibrosis, pancreatic steatosis, and dysregulation of other islet hormones such as glucagon and somatostatin [11].
  Level of evidence: 4. Percentage of agreement: 97.1 %
- DM type 1 and 2 patients should only be screened if they have symptoms or nutritional deficiencies consistent with PEI.(see Box1, Box2)
  Level of evidence: 3. Percentage of agreement: 94.2 %

3.11. PEI in other conditions

- Exocrine pancreatic function may be impaired with age. Low FE-1 levels have been reported in 21.7 % of subjects over 60 years and 11.5 % of people aged 50–75 years [2].
  Level of evidence: 4. Percentage of agreement: 93.9 %
- The clinical relevance of fatty pancreas and whether it can cause PEI is still unclear [2].
  Level of evidence: 4. Percentage of agreement: 95.3 %
- The prevalence and clinical relevance of PEI in hemochromatosis is not known [2].
  Level of evidence: 5. Percentage of agreement: 98.4 %
- Low FE-1 levels and pathological BT-PABA test results in new celiac disease (CeD) patients have been reported in 10.5–46.5 % (pooled prevalence 26.2 %). Testing for PEI should be considered if significant malnutrition is present at diagnosis of CeD or if there are persisting symptoms not responding to a gluten-free diet [2].

Box 1
The most important conclusions from the guidelines [2]:

1 The definition of PEI is a reduction in exocrine pancreatic secretion to a level that prevents normal digestion of nutrients. This has important clinical implications as the threshold for PEI can be influenced by several factors; therefore, reduced pancreatic secretion should not be considered as synonymous with PEI.
2 The second important consequence of this definition is that it challenges the existing scientific evidence on PEI. Many of the clinical studies on PEI use an abnormal result on a pancreatic secretion test, such as fecal elastase, as a criterion for defining PEI. As a result, patients with pancreatic dysfunction are often mistakenly diagnosed with PEI, leading to biased study results.
3 As tests to assess nutrient digestion are either cumbersome (e.g., coefficient of fat absorption) or of limited availability (e.g., 13C-MTG breath test), this guidelines propose, generally, the global assessment of PEI-related symptoms, nutritional status, and pancreatic secretion to diagnose PEI in an appropriate clinical scenario until simple and accurate digestion tests are widely available.
4 The different likelihood of PEI in different clinical conditions significantly influences the diagnostic approach to PEI in clinical practice. The specificities of the diagnosis of PEI in different diseases are presented in this document.
5 As a result of malabsorption of nutrients, abdominal and bowel symptoms and nutritional deficiencies are among the consequences of PEI that affect patients' quality of life and are associated with long-term malnutrition-related complications. Therefore, PEI always requires treatment, and relief of symptoms and normalization of nutritional status are the therapeutic goals.
6 In general, treatment of PEI is based on nutritional advice and support as well as PERT. The dose of PERT should be individualized and is likely to be influenced at least by the severity of PEI and dietary habits (amount, calorie intake, and fat content of food).
7 Although a starting dose of 40,000–50,000 units with main meals and half this dose with snacks is generally recommended for adult patients, this dose may be insufficient in some patients with more severe PEI, such as those with pancreatic cancer and after pancreatoduodenectomy or total pancreatectomy.

Box 2
The most important unmet needs in research, areas lacking scientific evidence, and future directions [2]:

1 Despite the large number of studies published, the scientific evidence on PEI is rather weak. The change in the concept of PEI, as a reduction of pancreatic secretion severe enough to affect the digestion of nutrients, means that a relevant proportion of the previously published studies no longer fits the new concept.
2 Considering the concept of PEI as reported in this guideline, the actual prevalence of PEI in various pancreatic diseases, pancreatic and gastrointestinal surgeries, and other clinical conditions remains largely unknown. Most studies rely on the results of the fecal elastase-1 (FE-1) test, which reflects pancreatic secretion but not the digestive capacity of the pancreas. Although the FE-1 test is rather sensitive for diagnosing PEI, its specificity is not higher than chance. PEI prevalence may be overestimated in different clinical scenarios. Therefore, there is a need for new epidemiological studies that include patients diagnosed with PEI based on current recommendations.
3 The development of a test or biomarker for the diagnosis of PEI is a pressing need. The coefficient of fat absorption (CFA) remains the reference method for the diagnosis of PEI; however, this test is cumbersome, unpleasant, and difficult for patients to comply with. The 13C-MTG breath test is a promising alternative to CFA, but it is currently only available in a limited number of countries and standardization is still required. Research into new biomarkers for PEI diagnosis should be encouraged.
4 Treatment of PEI is another area where there is still much unmet need. Except for clinical trials that have included patients based on CFA, most other therapeutic trials of PERT are biased by inappropriate inclusion of patients. On the contrary, the requirement to use CFA as the main outcome to evaluate the efficacy of PERT in patients with PEI significantly limits the inclusion of patients in clinical trials. In this context, use of the 13C-MTG breath test is much simpler and probably as effective as CFA, but it is not yet approved by the drug authorities. Other outcomes such as symptom relief, quality of life using patient reported outcome instruments, and nutritional improvement are clinically relevant.
5 Most of the available evidence on PERT is based on enzyme preparations containing small enteric-coated pellets of porcine origin. Other preparations, even commercially available in some countries, have received much less evaluation. Furthermore, due to the limited production capacity of porcine enzymes, new enzyme preparations from other sources are urgently needed.
6 The optimal and most effective enzyme dose in different diseases and clinical conditions, the relationship between enzyme dose and clinical effect, and the importance of modifying intraluminal pH on the efficacy of PERT are areas where more robust evidence is needed.

Level of evidence: 4. Percentage of agreement: 97.1 %

- Low FE-1 values have been reported in 0–41 % of patients with inflammatory bowel disease (IBD) and in 19 %–31 % of patients with autoimmune pancreatitis and IBD [2].
  Level of evidence: 4. Percentage of agreement: 93.9 %
- There is a symptomatic crossover between diarrhea-predominant irritable bowel syndrome (D-IBS) and PEI. Low FE-values have been reported in 4–13 % of patients with D-IBS. It is still unclear whether PEI coexists with IBS or causes symptoms suggesting IBS [2].
  Level of evidence: 4. Percentage of agreement: 88.1 %
- Low FE-1 values have been reported in 1–10 % of patients treated with immune-checkpoint inhibitors and tyrosine kinase inhibitors [2].
  Level of evidence: 4. Percentage of agreement: 95.2 %
- PEI can occur in patients with rare/inherited diseases such as Shwachman-Bodian-Diamond syndrome, Johanson-Blizzard syndrome, Pearson syndrome, Shteyer syndrome, and other rare inherited diseases. The prevalence of PEI in these rare inherited diseases is unknown due to their rarity [2].
  Level of evidence: 4. Percentage of agreement: 98.4 %
- Low FE-1 levels have been reported in 20–50 % of HIV patients. PEI in other infectious diseases is possible, but the prevalence is unknown [2].
  Level of evidence: 4. Percentage of agreement: 93.8 %
- The prevalence of PEI in chronic kidney disease has been reported in up to 72 % of patients. However, these studies were of low quality [2].
  Level of evidence: 4. Percentage of agreement: 92.3 %
- The prevalence of PEI varies from 8 to 24 % in patients treated with somatostatin analogues [2].
  Level of evidence: 4. Percentage of agreement: 98.5 %
- The prevalence of PEI in patients with pancreatic neoplasms other than ductal adenocarcinoma is unknown. Most studies of these patients report PEI after surgery. Patients with pancreatic neuroendocrine tumors may develop PEI, which may be due to long-term treatment with somatostatin analogues [2].
  Level of evidence: 4. Percentage of agreement: 92.5 %
- Low levels of FE-1 have been reported in 6.9–56.7 % of patients with chronic heart failure [2].
  Level of evidence: 4. Percentage of agreement: 88.9 %
- The prevalence of PEI in patients with Sjogren's syndrome varies widely, ranging from 0 % to 63 % depending on the method used for PEI diagnosis. However, the quality of the evidence is low [2].
  Level of evidence: 4. Percentage of agreement: 92.1 %

4. Conclusion

The definition, pathogenesis, clinical consequences, diagnosis, treatment, and monitoring of PEI in different clinical conditions have been systematically reviewed and consensus has been reached regarding these multidisciplinary, evidence-based European clinical guidelines [2]. The guidelines also highlight unmet needs and areas where the scientific evidence is weak or lacking, to guide future research in this area. PEI is associated with maldigestion and malabsorption of nutrients, resulting in symptoms of intestinal malabsorption and nutritional deficiencies that negatively impact patients' quality of life and are associated with long-term malnutrition-related complications and mortality. Along with appropriate management of the underlying condition causing PEI, knowledge of when and how to diagnose PEI, optimal therapy and therapeutic goals, and appropriate monitoring of patients are essential to reduce the risk of complications and improve the quality of life and survival of patients with PEI [2].

Acknowledgements

The authors would like to thank the member societies of United European Gastroenterology (UEG) for participating and endorsing these guidelines: European Digestive Surgery (EDS), European Society for Primary Care Gastroenterology (ESCPG), European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), European Society for Clinical Nutrition and Metabolism (ESPEN), European Society of Digestive Oncology (ESDO), and European Society of Primary Care Gastroenterology (ESPCG). We thank UEG for an unrestricted educational grant enabling the independent conduct of these guidelines. The authors are indebted to Dawn Swibold, general manager of the EPC, for assistance in developing these guidelines.

Appendix

Hana Algül[1], Livia Archibugi[2], Marianna Arvanitakis[3], Sorin Barbu[4], Georg Beyer[5], Mihailo Bezmarevic[6], Frank Bodewes[7], Marja A. Boermeester[8,9], Stefanos Bonovas[10], Dmitry Bordin[11], Marco Bruno[12], Djuna Cahen[12], Gabriele Capurso[13], Güralp Ceyhan[14], Laszlo Czako[15], Ferdinando D'Amico[13], Enrique De Madaria[16], Julian De Martino[17], Pierre H. Deprez[18], Christos Dervenis[19], Petr Dité[20], Asbjørn Drewes[21], Sinead N. Duggan[22], Deniz Duman[23], Trond Engjom[24], Nils Ewald[25,26], Ovidiu Fabian[4], Pierluigi Fracasso[27], Helmut Friess[28], Jens Brøndum Frøkjær[29], Luca Frulloni[30], Sebastien Gaujoux[31], Cristian Gheorghe[32], Sophie Gohy[33,34], Natalya Gubergrits[35], Philip Hardt[36], Truls Hauge[37,38], Peter Hegyi[39-42], Andrew Hopper[43], Pali Hungin[44], Julio Iglesias-Garcia[45], Jutta Keller[46], Mariia Kiriukova[47], Jörg Kleeff[48], Alexander Kleger[49,50], Andrea Laghi[51], José Larino-Noia[52], Johanna Laukkarinen[53,54], John Leeds[55,56], Björn Lindkvist[57], Etna Masip[58], Giovanni Marchegiani[59], Amir Mari[60], Emma Martinez-Moneo[61], Julia Mayerle[5], Anders Molven[62,63], Johann Ockenga[64], Alexey Okhlobystin[65], Salvatore Paiella[66], Nikola Panic[67], Andrea Parniczky[68,69], Lukas Perkhofer[70], Raffaele Pezzilli[71], Mary Phillips[72], Daniele Piovani[73], Goran Poropat[74,75], Jelena Rakic Matic[76], Vinciane Rebours[77], Keith Roberts[78], Stuart Robinson[79], Jonas Rosendahl[80], Roberto Salvia[66], Vasile Sandru[81,82], Alain Sauvanet[83], Isabelle Scheers[84], Alexander Schneider[85], Oleg Shvets[86], Serena Stigliano[87], Davor Stimac[88], Oliver Strobel[89], Andrea Szentesi[90], Hester Timmerhuis[91], Mihaela Udrescu[92], Szilard Vancsa[93], Vicki Veness[94], Michael Wilschanski[95], Heiko Witt[96]

Affiliations:

[1]Comprehensive Cancer Center Munich TUM, Institute for Tumor Metabolism, Technical University of Munich, Munich, Germany.

[2]Pancreatobiliary Endoscopy and Endosonography Division, Pancreas Translational & Clinical Research Center, IRCCS San Raffaele Scientific Institute, Milan, Italy; Vita-Salute San Raffaele University, Milan, Italy.

[3]Service de Gastroenterologie, d'Hepato-Pancreatologie et d'Oncologie digestive, Hopital Erasme, HUB, Bruxelles, Belgium.

[4]4th Surgery Department, University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca, Romania.

[5]Department of Medicine II, Ludwig Maximilian University Hospital, Munich, Germany.

[6]Department of Hepatobiliary and Pancreatic Surgery, Clinic for General Surgery, Military Medical Academy, University of Defense, Belgrade, Serbia.

[7]Division of Pediatric Gastroenterology/Hepatology, Beatrix Children's Hospital/University Medical Center Groningen, University of Groningen, Groningen, Netherlands.

[8]Amsterdam UMC Location University of Amsterdam, Department of Surgery, Meibergdreef 9, Amsterdam, The Netherlands.

[9]Amsterdam Gastroenterology, Endocrinology, & Metabolism, Amsterdam, Netherlands.

[10]Department of Biomedical Sciences, Humanitas University, Milan, Italy.

[11]Department of Upper Gastrointestinal, Pancreatic, and Biliary Diseases, A.S. Loginov Moscow Clinical Research Center, Moscow, Russia; Department of Outpatient Therapy and Family Medicine, Tver State Medical University, Tver, Russia.

[12]Department of Gastroenterology & Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands.

[13]Department of Gastroenterology, San Raffaele University Hospital, Milan, Italy.

[14]Department of General Surgery, HBP-Unit, School of Medicine, Acibadem Mehmet Ali Aydinlar University, Istanbul, Istanbul, Turkey.

[15]Center for Gastroenterology, University of Szeged, Szeged, Hungary.

[16]Department of Gastroenterology, Dr. Balmis General University Hospital-ISABIAL, Alicante, Spain.

[17]Department of Hepato-Biliary, Pancreatic Surgery and Liver Transplantation, Hôpital la PitiéSalpêtrière, AP-HP, Paris, France; Sorbonne Université, Paris, France.

[18]Department of Gastroenterology and Hepatology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium.

[19]Department of Surgery, AGIA OLGA Hospital, Athens, Greece.

[20]Internal Gastroenterology Clinic, University Hospital Brno; Brno; Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic.

[21]Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aalborg, Denmark.

[22]Center for Public Health, Institute of Clinical Sciences, Queen's University Belfast, Northern Ireland.

[23]Department of Gastroenterology, School of Medicine, Marmara University, Istanbul, Turkey.

[24]Department of Gastroenterology, Haukeland University Hospital, Bergen, Norway.

[25]Institute for Endocrinology, Diabetology and Metabolism, Johannes Wesling University Hospital Minden, Minden, Germany.

[26]Justus-Liebig University Giessen, Giessen, Germany.

[27]Department of Gastroenterology and Digestive Endoscopy, Ospedale Sandro Pertini, Local Health Agency Roma 2, Rome, Italy.

[28]Department of Surgery, TUM School of Medicine and Health, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany.

[29]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark and Department of Radiology, Aalborg University Hospital, Aalborg, Denmark.

[30]Department of Medicine, Pancreas Unit, University of Verona, Verona, Italy.

[31]Department of Hepato-Biliary, Pancreatic Surgery and Liver Transplantation, Hôpital la Pitié Salpêtrière, AP-HP, Paris, France; Sorbonne Université, Paris, France.

[32]Center of Gastroenterology & Hepatology, Fundeni Clinical Institute, "Carol Davila" University of Medicine, Bucharest, Romania.

[33]Department of Pneumology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium.

[34]Cystic Fibrosis Reference Center, Cliniques Universitaires Saint-Luc, Université Catholique de Louvai, Brussels, Belgium.

[35]Into-Sana Multi-Field Clinic, Odesa, Ukraine.

[36]Institute for Endocrinology, Diabetology, and Metabolism, Johannes Wesling University Hospital Minden, Minden, Germany; Justus-Liebig University Giessen, Giessen, Germany.

[37]Department of Gastroenterology, Oslo University Hospital, Ullevål, Norway.

[38]University of Oslo, Clinical Medicine, Oslo, Norway.

[39]Centre for Translational Medicine, Semmelweis University, Budapest, Hungary [4]

[0]Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary.

[41]Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary.

[42]Translational Pancreatology Research Group, Interdisciplinary Centre of Excellence for Research and Development and Innovation, University of Szeged, Szeged, Hungary.

[43]Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom.

[44]Faculty of Medical Sciences, Newcastle University, Newcastle-upon-Tyne, United Kingdom.

[45]Department of Gastroenterology and Hepatology, University Hospital of Santiago de Compostela, Spain.
[46]Department of Internal Medicine, Israelitic Hospital, Hamburg, Germany.
[47]Pancreatic, Biliary, and Upper GI Diseases Department, Moscow Clinical Scientific Center, Moscow, Russia.
[48]Department of Surgery, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany.
[49]Institute of Molecular Oncology and Stem Cell Biology (IMOS), Ulm University Hospital, Ulm, Germany.
[50]Division of Interdisciplinary Pancreatology, Department of Internal Medicine I, Ulm University Hospital, Ulm, Germany.
[51]Radiology Unit, Department of Medical Surgical Sciences and Translational Medicine, "Sapienza" Univeresity of Rome, Sant'Andrea University Hospital, Rome, Italy.
[52]Hospital Clinico Universitario de Santiago de Compostela, Santiago de Compostela, Spain.
[53]Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Finland.
[54]Tampere University, Faculty of Medicine and Health Technology, Tampere, Finland.
[55]HPB Unit and Department of Gastroenterology, Newcastle upon Tyne Hospitals NHS Foundation Trust, United Kingdom.
[56]Population Health Sciences Institute, Newcastle University, United Kingdom.
[57]Department of Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden.
[58]Hospital Universitari i Politecnic La Fe, Valencia, Spain.
[59]Department of Surgical, Oncological, and Gastroenterological Sciences, University of Padua, Padua, Italy.
[60]Gastroenterology Institute and Neurogastroenterology Unit, Nazareth Hospital, Nazareth, Israel; Bar Ilan Faculty of Medicine, Nazareth, Israel.
[61]Gastroenterology Department, University Hospital of Cruces, Barakaldo, Bizkaia, Spain.
[62]Gade Laboratory for Pathology, Department of Clinical Medicine, University of Bergen, Bergen, Norway.
[63]Section for Cancer Genomics, Haukeland University Hospital, Bergen, Norway.
[64]Department of Gastroenterology, Endocrinology and Clinical Nutrition, Klinikum Bremen Mitte, Bremen, Germany.
[65]Department of Internal Disease Propedeutics, Gastroenterology and Hepatology, I.M. Sechenov First Moscow State Medical University, Moscow, Russia.
[66]Unit of Pancreatic Surgery, University of Verona Hospital Trust, Verona, Italy.
[67]Faculty of Medicine, University of Belgrade, Belgrade, Serbia; Digestive Endoscopy Unit, University Clinic "Dr Dragisa Misovic-Dedinje", Belgrade, Serbia.
[68]Heim Pal National Pediatric Institute, Budapest, Hungary.
[69]Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary.
[70]Section of Interdisciplinary Pancreatology, Department of Internal Medicine I, Ulm University Hospital, Ulm, Germany.
[71]Potenza Medical County Association, Potenza, Italy.
[72]Department of Nutrition and Dietetics, Royal Surrey County Hospital, NHS Foundation Trust, Guildford, United Kingdom.
[73]Department of Biomedical Sciences, Humanitas University, Milan, Italy.
[74]Department of Gastroenterology, Clinical Hospital Center Rijeka, Rijeka, Croatia.
[75]Department of Internal Medicine, Faculty of Medicine of the University of Rijeka, Rijeka, Croatia.
[76]Health Center Zagreb West, Zagreb, Croatia.
[77]Department of Pancreatology, Beaujon Hospital, DMU Digest, AP-HP, Clichy, France.
[78]Department of HPB Surgery, University Hospitals Birmingham NHS Foundation Trust, University of Birmingham, United Kingdom.
[79]Department of Hepatobiliary, Pancreatic and Transplant Surgery, Department of Surgery, Freeman Hospital, Newcastle Upon Tyne, United Kingdom.
[80]Department of Internal Medicine I, Martin Luther University, Halle, Germany.
[81]Clinical Department of Gastroenterology, Bucharest Emergency Clinical Hospital; Bucharest, Romania.
[82]Department of Gastroenterology, University of Medicine and Pharmacy "Carol Davila" Bucharest, Bucharest, Romania.
[83]Department of Hepato-Biliary and Pancreatic Surgery and Liver Transplantation, Hopital Beaujon, AP-HP, Clichy, France & Université de Paris Cité, Paris, France.
[84]Department of Gastroenterology and Hepatology, Medical Center Bad Hersfeld-Rotenburg, Bad Hersfeld, Germany.
[85]Department of Gastroenterology and Hepatology, Medical Center Bad Hersfeld-Rotenburg, Bad Hersfeld, Germany.
[86]Department of Health and Nutrition, National University of Life and Environmental Sciences of Ukraine.
[87]Therapeutic Digestive Endoscopy Unit, Fondazione Policlinico Universitartio Campus BioMedico, Rome.
[88]Specialty Hospital Medico, Faculty of Medicine, University of Rijeka, Rijeka, Croatia.
[89]Department of General Surgery, Division of Visceral Surgery, Medical University of Vienna, Vienna, Austria.
[90]Institute for Translational Medicine, Medical School, University of Pécs, Hungary.
[91]Department of Surgery, St. Antonius Hospital Location Nieuwegein, The Netherlands.
[92]CMI Dr. Udrescu Mihaela, Bucharest, Romania.
[93]Centre for Translational Medicine, Semmelweis University, Budapest, Hungary.
[94]Department of Nutrition and Dietetics, Royal Surrey County Hospital, NHS Foundation Trust, Guildford, United Kingdom.
[95]Pediatric Gastroenterology, Hadassah Hebrew University Medical Center, Jerusalem, Israel.
[96]Pediatric Nutritional Medicine & Else Kröner-Fresenius-Centre for Nutritional Medicine (EKFZ), Technical University Munich (TUM), Freising, Germany.

References

[1] DiMagno EP, Go VL, Summerskill WH. Relations between pancreatic enzyme ouputs and malabsorption in severe pancreatic insufficiency. N Engl J Med 1973;288(16):813–5.
[2] Dominguez-Muñoz JE, Vujasinovic M, de la Iglesia D, et al. European guidelines for the diagnosis and treatment of pancreatic exocrine insufficiency: UEG, EPC, EDS, ESPEN, ESPGHAN, ESDO, and ESPCG evidence-based recommendations. United European Gastroenterol J 2025;13(1):125–72.
[3] Speckman RA, Friedly JL. Asking structured, answerable clinical questions using the population, intervention/comparator, outcome (PICO) framework. Pharm Manag PM R 2019;11(5):548–53.
[4] Howick J, Chalmers I, Glasziou P, et al. Oxford centre for evidence-based medicine 2011 levels of evidence. Centre for Evidence-Based Medicine; 2011. *Retrieved July from*.
[5] Boltin D, Lambregts DM, Jones F, et al. UEG framework for the development of high-quality clinical guidelines. United European Gastroenterol J 2020;8(8):851–64.
[6] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336(7650):924–6.
[7] Löhr JM, Beuers U, Vujasinovic M, et al. European Guideline on IgG4-related digestive disease – UEG and SGF evidence-based recommendations. UEG J 2020;8(6):637–66.
[8] Löhr JM, Dominguez-Munoz E, Rosendahl J, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United European Gastroenterol J 2017;5(2):153–99.
[9] Dominguez-Munoz JE, Drewes AM, Lindkvist B, et al. Recommendations from the United European Gastroenterology evidence-based guidelines for the

diagnosis and therapy of chronic pancreatitis. Pancreatology 2018;18(8):847–54.
[10] de-Madaria E, Abad-Gonzalez A, Aparicio JR, et al. The Spanish Pancreatic Club's recommendations for the diagnosis and treatment of chronic pancreatitis: part 2 (treatment). Pancreatology 2013;13(1):18–28.
[11] Zsóri G, Illés D, Terzin V, Iványi E, Czakó L. Exocrine pancreatic insufficiency in type 1 and type 2 diabetes mellitus: do we need to treat it? A systematic review. Pancreatology 2018;18(5):559–65.
[12] Anoop S, Dasgupta R, Jebasingh FK, et al. Exocrine pancreatic insufficiency related fat malabsorption and its association with autonomic neuropathy in Asian Indians with type 2 diabetes mellitus. Diabetes Metabol Syndr 2021;15(5):102273.