**TITLE:**

# EVIDENCE-BASED GUIDELINES FOR THE MANAGEMENT OF PANCREATIC EXOCRINE INSUFFICIENCY AFTER PANCREATIC SURGERY.

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**Statement**

Reprints will not be available from the author(s)

**Running Head**

Guidelines for PEI after pancreatic surgery

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**Mini-Abstract**

Exocrine pancreatic insufficiency is a frequent complication after pancreatic surgery but there is a lack of evidence-based recommendations for the diagnosis and management of this disorder.

**STRUCTURED ABSTRACT**

Objective: To provide evidence-based recommendations for the management of exocrine pancreatic insufficiency (EPI) after pancreatic surgery.

Background: EPI is a common complication after pancreatic surgery but there is certain confusion about its frequency, optimal methods of diagnosis and when and how to treat these patients.

Methods: Eighteen multidisciplinary reviewers performed a systematic review on 10 predefined questions following the GRADE methodology. Six external expert referees reviewed the retrieved information. Members from AESPANC were invited to suggest modifications and voted for the quantification of agreement.

Results: These guidelines analyze the definition of EPI after pancreatic surgery, (1 question), its frequency after specific techniques and underlying disease (4 questions), its clinical consequences (1 question), diagnosis (1 question), when and how to treat post-surgical EPI (2 questions) and its impact on the quality of life (1 question). Eleven statements answering those 10 questions were provided: 1 (9.1%) was rated as a strong recommendation according to GRADE, 3 (27.3%) as moderate and 7 (63.6%) as weak. All statements had strong agreement.

Conclusions: EPI is a frequent but under-recognized complication of pancreatic surgery. These guidelines provide evidence-based recommendations for the definition, diagnosis and management of EPI after pancreatic surgery.

## INTRODUCTION

Exocrine pancreatic insufficiency (EPI) is a common complication after pancreatic surgery. Depending on the underlying disease, type of surgical procedure, extent of pancreatic resection and anatomical reconstruction, EPI may vary in frequency and severity. Despite the large amount of information dealing with general postoperative complications, there is a lack of well-designed studies investigating EPI. This has led to a certain degree of confusion about the frequency of EPI after surgery, its optimal methods of diagnosis and when and how to treat these patients. The aim of these guidelines is to provide evidence-based recommendations for the diagnosis and treatment of EPI after pancreatic surgery.

## METHODS

The Spanish Association of Pancreatology (AESPANC) led the initiative and chose two coordinators (EdM and LS) who developed the methodology, suggested the reviewers and wrote the initial version of the working plan. Eighteen Spanish primary reviewers were chosen, based on their expertise in pancreatic surgery, clinical pancreatology or nutrition (9 surgeons, 8 gastroenterologists and 1 endocrinologist). A group of external expert referees, composed by 3 pancreatic surgeons and 3 gastroenterologists, were invited to participate in the project. These referees were selected among internationally renowned researchers in pancreatology. A draft of the questions to be addressed was proposed by the coordinators and discussed by the whole team (via e-mail) finally resulting in 10 questions.

The coordinators assigned each question to 2 or 3 primary reviewers, based on their expertise. A working plan for the systematic review was provided, inspired by the IAP/APA evidence-based guidelines for the management of acute pancreatitis (1). All reviewers were asked to take a GRADE system tutorial (link on UpToDate: http://www.uptodate.com/home/grading-tutorial).

The systematic research for suitable articles was performed in the PubMed and Cochrane databases without language restriction. The authors were provided with a search algorithm for

each question (see supplementary material 1). Additionally, studies from the citations of the reviewed articles could also be included.

The inclusion criteria to select the articles were as follows: observational studies, clinical trials and meta-analysis/systematic reviews relevant to the specific question. Studies published only as abstracts were excluded.

The primary reviewers were asked to write a report including:

1. A table with a structured summary of the included studies (authors, journal, date of publication, design, population, definition of outcome variable, results and comments).

2. An evidence-based statement to the study question.

3. The strength of the recommendation (1=strong, 2=weak) and quality of evidence (A = high, B = moderate, C = low) according to the GRADE guidelines as adapted for "UpToDate" (Table 1).

4. Remarks: a brief (up to 750 words) commentary explaining current evidence to support the recommendation.

The external expert referees were asked to review the report of the primary reviewers; their task was to check that:

1. There was no relevant study missing.

2. Included studies met the eligible criteria.

3. There was no mistake in the report of the included studies.

4. The strength of recommendation was adequate according to the retrieved evidence.

With the retrieved information by primary reviewers and external expert referees, the coordinators wrote a first draft of the manuscript, including the statement, strength of recommendation quality of evidence and remarks for every question. This draft was reviewed by the whole team and afterwards shared electronically with the members of AESPANC. Following the methodology used in the IAP/APA evidence-based guidelines for the management of acute pancreatitis (1) the members of AESPANC voted on a five point Likert scale (A: "definitely yes", B: "probably yes", C: "no specific recommendation", D: "probably no", E: "definitely no") on the statements and their GRADE score. It was defined that "strong agreement" would require at

least 70% of votes to be either “definitely yes” or “probably yes”. The members of AESPANC also had the possibility of making suggestions in open text for every question, aiming not to modify the statement but to include clinically relevant remarks.

With the feedback from AESPANC members the coordinators wrote the second draft of the manuscript, that was shared again with the primary reviewers and with the external expert referees for suggestions and final approval.

## RESULTS

### Question 1

**What is the definition of EPI after pancreatic surgery?**

**Statement**

EPI after pancreatic surgery is defined as the condition in which the amount of secreted pancreatic enzymes is not enough to maintain a normal digestion due to modifications of gastrointestinal anatomy together with functional changes due to underlying pancreatic disease, extent of pancreatic tissue removed, reduced postprandial stimulation and asynchrony between gastric emptying of nutrients and pancreatic enzyme secretion.

**Strength of the recommendation and quality of evidence: 1C.**

**Strong agreement (A: 87.5%; B: 12.5%)**

**Remarks**

There is no widely accepted consensus definition of EPI, and there are no studies aiming to validate different EPI definitions with outcome variables after pancreatic surgery. Published studies addressing EPI after surgery have different definitions according to the different pancreatic function test (PFT) used in each particular study (faecal elastase, coefficient of fat absorption, breath test ... etc.). Currently, from a pragmatic point of view, EPI may be defined as the situation in which the disturbance of pancreatic function is associated with the inability of the pancreas to perform normal digestion (2). Thus an abnormally high faecal fat excretion (FFE) (>7g/day) or a Coefficient of Fat Absorption (CFA) <93% (equivalent to a FFE>7g/day under a diet containing 100 g of fat/day) is characteristically indicative of EPI in clinical practice (2-4) and

should be considered as a gold standard. EPI after surgery may be secondary to a reduced pancreatic secretion due to the underlying pancreatic disease (3, 5), extent of pancreatic resection (6), reduced postprandial stimulation (7, 8), and gastrointestinal anatomical changes leading to an asynchrony between gastric emptying of nutrients and enzyme secretion (9).

**Question 2**

**What is the frequency of EPI in patients with acute pancreatitis after pancreatic necrosectomy?**

**Statement**

The frequency of EPI in patients with acute pancreatitis after necrosectomy is variable due to significant heterogeneity in the design and population of available studies addressing this issue. Pancreatic function tends to improve and consequently frequency of EPI diminishes over time after necrosectomy. About a quarter of patients with acute necrotizing pancreatitis present EPI after pancreatic necrosectomy.

**Strength of the recommendation and quality of evidence: 1C**

**Strong agreement (A: 45%; B: 55%)**

**Remarks**

Several factors can explain the wide range of frequency of EPI after necrosectomy reported in the available studies: 1) differences among the definition of EPI and tests used to assess pancreatic function; 2) different intervals at which such tests were performed after necrosectomy; 3) variability in the proportion of alcoholic-related acute pancreatitis (AP)(10);

4) the indication to perform PFT: some studies included the entire sample of patients while in others PFT were only carried out in patients with symptoms suggesting maldigestion, and finally there are studies reporting only the frequency of clinical steatorrhea.

Some studies used FFE to assess pancreatic function and define EPI as FFE > 7 g/24 h. Gupta et al. (11) reported increased FFE in 6 out of 21 patients (28.6 %) at least 6 months after necrosectomy. Sabater et al. (12) compared exocrine pancreatic function in patients with severe biliary AP with and without necrosectomy. Pancreatic function was assessed by FFE, faecal

chymotrypsin and secretin-cerulein test (SCT), 12 months after AP. Seven out of 12 patients with necrosectomy (58.3 %) had abnormal PFT, with steatorrhea in 3 patients (25 %). Reddy et al. (10) reported increased FFE in 8 out of 10 (80 %) patients with necrosectomy, but no patient had symptoms of steatorrhea or EPI. Tsiotos et al. (13) and Bavare et al. (14) defined EPI with FFE, but it was only performed in patients with significant changes in bowel habit; thus, the prevalence of EPI could be underestimated. Tsiotos et al. (13) reported EPI in 11 out of 44 patients with acute necrotizing pancreatitis (ANP) and necrosectomy (25 %) and EPI tended to remain stable or improve clinically over time. Bavare et al (14) evaluated the patients at different time points: 13 out of 18 (72.2 %) had EPI at discharge, 50 % had EPI at 6 months, and at 18 months 2 patients (11.1 %) presented EPI.

In the study by Reszetow et al. (15), EPI was defined according to faecal elastase test (FE-1), measured at a median of 61 months after biliary ANP. Four out of 18 (22.2%) alcoholic ANP patients had moderate EPI versus none in the biliary group. It must be taken into account that 44 % of alcoholic ANP patients had pancreatic calcifications in follow-up. Bozkhurt et al. (16) performed the Lundh test after ANP in 53 patients (73% of them had open necrosectomy). EPI was present in all patients at 1-3 months and in 86 % at 3-6 months; 26 % had severe EPI at 1-3 months and 6 % at 18 months. Unfortunately the authors did not distinguished between operated and non-operated patients and some patients had morphological signs of chronic pancreatitis. Angelini et al. (17) reported EPI (evaluated with SCT) in 8 out of 20 patients with necrosectomy (40 %) at 12-36 months and in 6.6 % at 36-48 months after the onset of disease. Seligson et al. (18) detected EPI in 7/10 (70 %) patients with Lundh Test. In some studies, EPI was reported on the basis of need for pancreatic enzymes or clinical symptoms of steatorrhea, with figures between 23% (19) and 25% (20) respectively.

**Question 3**

**What is the frequency of EPI in patients with chronic pancreatitis after pancreatic surgery?**

**Statement**

The incidence of EPI in patients with chronic pancreatitis after derivative surgery or hybrid procedures is the following: after Partington-Rochelle procedure there are clinical steatorrhea and/or other clinical symptoms in 0-32% of patients and altered PFT in 80 %; after Frey procedure there are clinical steatorrhea and/or other clinical symptoms in 33% of patients and altered PFT in 86%; after duodenum preserving pancreatic head resection (DPPHR) there are clinical steatorrhea and/or other clinical symptoms in 26-34% of patients and altered PFT in more than 80% of patients.

The incidence of EPI following pancreatoduodenectomy (PD) for chronic pancreatitis is high, within the range of 35-100%, most of the studies showing >60%. The incidence of EPI following distal pancreatectomy (DP) for chronic pancreatitis seems to be lower, ranging from 27.5 to 63%.

Since there is a high prevalence of EPI in chronic pancreatitis patients, and few studies evaluate EPI before pancreatic surgery, the specific contribution of the surgical procedure to EPI is difficult to quantify.

**Strength of the recommendation and quality of evidence: 1C**

**Strong agreement (A: 52.5%; B: 45%; C: 2.5%)**

**Remarks.**

The studies addressing EPI in patients with chronic pancreatitis after derivative surgery or hybrid procedures can be divided into 5 groups: papers comparing Partington-Rochelle versus PD (21-24); papers comparing Frey versus PD (25-27); papers comparing DPPHR vs PD (28-35); papers comparing DPPHR vs Frey procedure (36, 37) and miscellaneous retrospective series (38-40). Several biases have been detected. Firstly, the definition of EPI has been established following a wide variety of PFTs with a lack of studies using FFE, too many definitions that probably contribute to the high variability in the prevalence of EPI. Secondly, the proportion of patients with preoperative EPI is not well defined, thus it is not possible to know whether the occurrence of postoperative EPI is due to the surgical procedure or is a consequence of the underlying disease. Thirdly, the type of available studies: there are 2 meta-analyses which

include only 3 and 4 papers respectively; 10 studies are retrospective or cross sectional studies; 11 are prospective studies (9 randomised controlled trials (RCT) and 2 non-randomised studies); some papers show long term follow-up results of previous RCT. The two meta-analyses covering this topic had very few patients and different definitions of EPI (31, 34). Fourthly, some series show a high loss of patients in follow up and, additionally, papers are not focused on EPI but compare different results of morbidity and mortality between two techniques.

Regarding the frequency of EPI in patients with chronic pancreatitis after resectional procedures (PD, DP), four prospective RCT (27, 29, 30, 33) (two of them with long-term follow-up), two prospective non-randomised studies (25, 28), two meta-analyses (31, 34) and 10 retrospective studies (21-23, 26, 32, 39, 41-44) were included. The incidence of EPI after PD operation ranged from 35 to 100%. However, some concerns can be raised as to the quality of these findings. Firstly, EPI was not the primary outcome in the majority of these studies, which were mainly designed to compare different surgical techniques. Furthermore, definition of EPI was not homogeneous and it seems that clinical definition (expressed by questionnaire or need for pancreatic enzymes) detected a generally lower number of patients with EPI when compared to PFT. Secondly, in most non-randomised studies, Whipple's operation was performed when pancreatic cancer was suspected or pancreatic duct was not dilated, causing an important selection bias. Finally, preoperative assessment of EPI was scarcely performed and high variability was reported among studies. Except for one study (41), surgery always increased the incidence of EPI. The two meta-analyses (31, 34) do not report any definition of EPI, hence making interpretation difficult. The only study that seems to avoid the previously mentioned biases is Izbicki's RCT (45), whose long-term results have been reported by Bachmann et al (27). This study shows that the incidence of EPI is 93% with a 15 year follow-up and thus this value should be taken into account when predicting the occurrence of EPI following PD for chronic pancreatitis. Regarding DP, the incidence of EPI ranged from 27.5 % to 63%. As mentioned before, the definition of EPI and the scarce preoperative assessment

of pancreatic function can be considered strong biases.

**Question 4**

**What is the frequency of EPI in patients with pancreatic tumours after resection (PD, DP)?**

**Statement**

The incidence of EPI following PD for pancreatic tumours is high, especially in patients undergoing PD due to malignancy, with a range of 64-100 %. The incidence of EPI after DP is lower than after PD, within a range of 0-42%.

**Strength of the recommendation and quality of evidence: 1C**

**Strong agreement (A: 67.5%; B: 32.5%)**

**Remarks**

Information regarding the incidence of EPI in patients with pancreatic tumours after resection is limited and there is a lack of well-designed studies. Most available studies are retrospective and cross-sectional, limited by small sample size and single-institution designs; they also include a heterogeneous patient population with malignant and benign diseases. They include different types of surgery: PD, DP as well as atypical resections. Additionally, most of the reports include patients with and without chronic pancreatitis, and have used different methods to assess the pancreatic exocrine function.

Twenty-two studies have described the impairment of exocrine function after pancreatic head resection (4-6, 46-64): fourteen studies included only patients who underwent PD (5, 49, 51, 53-60, 62-64), seven studies included both PD and DP (4, 6, 46, 47, 50, 52, 61)(central or total pancreatectomy in three of them (47, 50, 52)), and one study included PD and total pancreatectomy (48). Fourteen studies included a heterogeneous patient population with malignant and benign diseases (6, 47-51, 53-57, 59-61), five studies included only patients with malignant disease (4, 5, 46, 58, 63), and one study covered only benign tumours (52). There was also one meta-analysis (65).

Among the studies, seven different methods for the assessment of EPI were applied: 10 studies (4, 5, 46-48, 54, 55, 57-59) used FE-1, two studies (50, 52) used faecal chymotrypsin

levels, four studies (49, 53, 56, 63) used clinical steatorrhea, three studies (6, 51, 64) used $^{13}$C-labelled mixed triglyceride breath test ($^{13}$C-MTG), three studies (60-62) used urinary PABA excretion rate, one study (4) used coefficient of fat absorption, and two studies (48, 59) used FFE (Van de Kamer method). Depending on the method used to evaluate exocrine pancreatic function, results vary considerably (Table 2).

EPI rates varied widely from 24 to 100%. When only considering patients who underwent PD for malignant disease, EPI was present in 64-100% (4, 5, 46, 58). Five studies (46, 52, 55, 60, 61) have evaluated the preoperative and postoperative exocrine function. In the study by Sikkens et al (46), EPI was present in 44.8% at the time of diagnosis of pancreatic cancer increasing to 89% at the end of follow-up. However, follow-up was limited to 6 months, the long-term course was not evaluated, and the study covered two types of surgery (DP and PD. In the series by Falconi et al (52) including 51 PD for benign tumours with normal preoperative pancreatic exocrine function, EPI was observed in 33% at the end of follow- up. Matsumoto and Traverso (55) reported a preoperative EPI rate of 33% (68% in pancreatic adenocarcinoma, and 46% in malignant vs 21% in benign disease), increasing to 73% after one year. In the study of Sato et al (61), the frequency of EPI increased from 44% in the preoperative period to 81% after pancreatic resection, but follow-up was limited to only 2 months. One study (60) suggested that postoperative impairment of pancreatic exocrine function was transient and reversible. EPI was present in 46% preoperatively, rose to 75% at the short-term (within 2 months), and then decreased to 33% after 12 months, but this observation was based on data from only 9 patients. Furthermore, the study included a heterogeneous group of patients with malignant and benign diseases.

Regarding DP, the incidence of EPI varied from 0-42% depending on the method used to assess pancreatic exocrine function. Similar biases can be observed in the studies evaluating this procedure as in PD and in fact most of the studies include both PD and DP (4, 6, 46, 47, 50, 52, 61). One study (66) showed that most patients who underwent DP for benign or malignant pancreatic disease did not experience permanent postoperative EPI: all patients had normal

exocrine function after DP or extended DP at 24 months after surgery and in the few cases where lower values were observed at 3 and 12 months after DP, the effect was transient. In the study by Falconi et al (52) including 50 left pancreatectomies for benign tumours with normal preoperative faecal chymotrypsin levels, 18% presented EPI at the end of follow-up. Sato et al (61) studied 12 patients who underwent DP for benign or malignant tumours of the pancreas and did not observe a significant decline in exocrine function after DP. In the meta- analysis of Xu et al (65), comparing central pancreatectomy with DP, 333 patients with benign or low grade malignant pancreatic lesions undergoing DP with exocrine function assessment were included and the EPI rate was 10.8%.

**Question 5**

**What is the frequency of EPI in patients with central pancreatectomy?**

**Statement**

Central pancreatectomy is a conservative resectional procedure that is associated with low rates of EPI, approximately 10%

**Strength of the recommendation and quality of evidence: 1C**

**Strong agreement (A: 62.5%; B: 35%; D: 2.5%)**

**Remarks**

Central (also known as medial) pancreatectomy (CeP) is a conservative, parenchyma-sparing technique aimed at preserving endocrine and exocrine pancreatic function by maintaining as much pancreatic tissue as possible. It also allows sparing the spleen from resection, which is beneficial for the immune system.

Studies addressing EPI in CeP have 2 important shortcomings: 1) with two exceptions (67, 68) the studies addressing EPI in CeP are retrospective 2) most studies do not report PFT in patients with CeP and most reports of EPI are based on clinical suspicion of steatorrhea and/or need for enzymes. Furthermore the only two prospective studies (67, 68) did not perform PFT on patients with CeP.

Two studies reported FFE after CeP in patients with benign/low grade pancreatic tumours

resulting in only 1 among 28 (3.6%) patients with EPI (69, 70). In seven studies other PFT were performed after CeP (50, 52, 71-75) reporting a range of EPI between 0 (52, 71, 73, 74) and 21% (75). Studies reporting clinical EPI (steatorrhea and/or weight loss and/or need for enzymes) describe a range between 0 % (76-85) and 43% (68). In a systematic review published in 2013, which included 21 studies, EPI (diagnosed either clinically or by means of diverse PFT) was noted in 9.9% of the patients (86).

In some studies, CeP was compared to other techniques by means of matched controls. CeP was not associated to significantly lower incidence of EPI than DP in six studies (50, 67, 74, 78, 87, 88) but another one (89) reported significant differences (lower EPI in CeP); in another paper a lower incidence of EPI compared to classic and pylorus-preserving-PD was reported (73) and also a lower incidence in CeP than in right resection in two studies (50, 90). In one recent study CeP and enucleation (considered jointly as "atypical resections") were associated with lower incidence of EPI than PD and left pancreatectomy, but specific data on CeP was not given (52). A recent systematic review found that CeP had a non-significant trend towards a lower incidence of EPI than DP (86), but another review reported a relative risk of EPI in CeP of 0.53 (95% confidence interval 0.32-0.86) when compared to DP (65).

**Question 6**

**What are the clinical consequences of EPI?**

**Statement**

EPI after pancreatic surgery may be subclinical or associated to symptoms secondary to the presence of undigested food in the intestinal lumen (fatty diarrhoea, flatulence, dyspeptic symptoms) and/or those associated with the loss of nutrients (weight loss, fat-soluble vitamin deficit).

**Strength of the recommendation and quality of evidence: 1C**

**Strong agreement (A: 77.5%; B: 17.5%; C: 2.5%; D: 2.5%)**

**Remarks**

EPI after pancreatic surgery is associated to abnormal total energy absorption due to

decreased digestion of fat, proteins and carbohydrates (91). EPI may be subclinical or associated to two kinds of symptoms: those associated with the presence of undigested food within the intestinal lumen (fatty diarrhoea, flatulence, dyspeptic symptoms) (92) and those associated with the loss of nutrients (mainly weight loss and fat-soluble vitamin deficit). The pancreas is involved in the digestion of proteins, carbohydrates, fat and other nutrients, but pancreatic lipase is so essential for fat absorption that most of the clinical consequences of EPI are related to fat maldigestion. The extent of malabsorption depends on the original disease process and the type and extent of surgical resection (93). The main clinical manifestation of fat malabsorption is steatorrhea typically reported as an increase in bowel movements, particularly after fatty meals, with loose, greasy, foul-smelling voluminous stools (94, 95). Steatorrhea, however, may be not present or present due to another cause. Postprandial abdominal pain and abdominal bloating may also be associated with EPI (95).

In patients with untreated EPI, potential additional complications such as weight loss, poor wound healing, vitamin deficiencies, osteomalacia, osteoporosis and low-trauma fractures, electrolyte imbalance, increased adverse effects of oncological treatments and lethargy can theoretically appear. One study compared pancreatic enzymes and placebo after surgery for chronic pancreatitis; 4 out of 5 patients receiving pancreatic enzymes gained weight but none of those 6 patients receiving placebo did (91). Apart from weight loss, there are no specific studies demonstrating a different nutritional status in patients with or without EPI after pancreatic surgery (4, 46).

**Question 7**

**What is the optimal method for the diagnosis of EPI after pancreatic surgery?**

**Statement**

PFT are of limited clinical value after pancreatic surgery since the prevalence of EPI is high and PFT are either difficult to perform or have poor predictive values. In cases when objective evidence for EPI is needed, FFE may be considered as the gold standard. Human elastase-1 (FE1) is easy to perform, has a high sensitivity to detect steatorrhea but its specificity seems

lower. The $^{13}$C-MTG may be an alternative method but further studies are needed. The absence of clinical symptoms of steatorrhea is an inaccurate method to rule out the existence of EPI.

**Strength of the recommendation and quality of evidence: 2B**

**Strong agreement (A: 35%; B: 40%; C: 22.5%; E: 2.5%)**

**Remarks**

Currently FFE/CFA may be considered as a gold standard for EPI (see question 1). Unfortunately this technique is cumbersome to perform: it requires a specific diet with a given amount of fat per day and stools from 3 days must be collected and processed. For these reasons it would be very useful to have simpler PFTs like FE-1 and/or $^{13}$C-MTG but few studies have tried to validate them for the diagnosis of steatorrhea by means of FFE or CFA after pancreatic surgery (4, 48). Halloran et al (4), studied 40 operated patients for pancreatic cancer (37 PD and only 3 left pancreatectomies) by FE-1 and CFA. A comparison of FE-1 using a cut-off point of 200 microg/g for EPI against CFA showed a diagnostic accuracy of 70%, with a sensitivity of 91%, a specificity of 35%, a positive predictive value of 70%, and a negative predictive value of 71% for FE-1. A ROC curve was generated, showing that the optimal cut-off for FE-1 (to diagnose EPI as defined by a CFA<93%) should be at 128 microg/g; area under the ROC curve (AUC) was 0,71, with a sensitivity of 90%, a specificity of 44%, a positive predictive value of 75% and a negative predictive value of 71%. Furthermore, there was no clear association between CFA and FE-1 levels. Overall, this study suggests the limited accuracy of FE-1 to diagnose EPI after pancreatic surgery. In another study Benini et al (48) studied 40 operated patients (37 pylorus preserving PD, 1 Whipple procedure and 2 total pancreatectomies) and 42 non-operated patients with pancreatic diseases, and evaluated EPI by FE-1 compared with FFE. Sensitivity and specificity of FE-1 in operated patients to detect steatorrhea were as follows: 100% and 83.3% for FE-1<200 mcg/g; 100% and 100% for FE- 1<100 mcg/g and 61.8% and 100% for FE-1<15 mcg/g. The cut-off for FE-1 in the diagnosis of EPI was considerably higher in operated compared to non-operated patients. Another conclusion of this study is that the relationship between both tests is not linear but logarithmic. The rate of increase of 24h

faecal fat output with decreasing FE-1 levels is not constant but depends on FE-1 values, with rates much higher when FE-1 values are low. The information regarding the correlation between FE-1 and FFE in left pancreatectomy is lacking. Nakamura et al. (96) investigated the usefulness of $^{13}$C-MTG compared with FE-1 concentration, but they used clinical steatorrhea as a gold standard. According to their results the $^{13}$C-MTG might be more useful than the FE-1 for the diagnosis of EPI after pancreatic surgery due to its higher accuracy, which could be explained by the fact that faecal water content influences the faecal enzyme concentration, resulting in falsely decreased FE-1 levels.

To sum-up we need more studies to validate the use of FE-1 (which was associated to a poor correlation with FFE in 2 studies and poor accuracy for the diagnosis of steatorrhea in one of them) and $^{13}$C-MTG in surgical patients. In this scenario the diagnosis of EPI may be assumed in patients with symptoms suggesting malabsortion. On the other hand the absence of clinical symptoms of steatorrhea is not an accurate method to exclude the existence of EPI (2, 10), and therefore PFT have a role in the diagnosis of EPI in asymptomatic patients.

**Question 8**

**When should EPI be treated?**

**Statement**

Pancreatic enzyme replacement therapy (PERT) should start once EPI is diagnosed or when there is a high clinical suspicion of EPI.

**Strength of the recommendation and quality of evidence: 2B Strong**

**agreement (A: 72.5%; B: 25%; C: 2.5%)**

**Remarks**

There is a paucity of high quality trials specifically designed to assess when to treat EPI in patients with previous pancreatic surgery. Most recommendations come from expert opinion or guidelines from medical societies (9, 95, 97-100).

The incidence of EPI associated with different surgical techniques, its clinical consequences and diagnosis have been addressed in specific questions in this review. As a summary,

deterioration of pancreatic function frequently occurs after pancreatic surgery; this condition is associated to relevant consequences. In patients with pancreatic surgery and EPI, PERT improves the CFA, the coefficient of nitrogen absorption, and reduces flatulence, diarrhoea and abdominal pain (91, 92, 101, 102) and therefore EPI should be treated as soon as it is diagnosed. However, the task of establishing the diagnosis of EPI in patients with previous pancreatic surgery does not have a straightforward approach (48). To overcome this limitation in patients with a high clinical suspicion of EPI, its diagnosis may be accepted after an empiric therapeutic trial showing that symptoms, nutritional markers or body weight improve after PERT.

**Question 9.**

**How should EPI be treated and how should follow-up be performed?**

**Statement A**

EPI after pancreatic surgery should be treated with PERT with pancreatin in form of enteric-coated minimicrospheres. Enzyme doses of 72,000-75,000 Ph.U.of lipase with main meals and 36,000-50,000 Ph.U. with snacks have shown to be effective in terms of improvement in fat digestion.

**Strength of the recommendation and quality of evidence: 1A.**

**Strong agreement (A: 70%; B: 27.5%; D: 2.5%)**

**Statement B**

Follow-up should be based on symptoms and nutritional evaluation, including body weight and routine nutritional parameters in blood

**Strength of the recommendation and quality of evidence: 2C. Strong**

**agreement (A: 70%; B: 27.5%; D: 2.5%)**

**Remarks**

Treatment of EPI after any pancreatic surgical procedure should be based on oral PERT (92, 101, 103). Enzyme doses of 72,000-75,000 Ph.U.of lipase with main meals and 36,000-50,000 Ph.U. with snacks have shown to be effective in terms of improvement in fat digestion in RCTs

(92, 103). Only 2 double-blind RCTs evaluating PERT for EPI in patients after pancreatic surgery have been reported (92, 103). An open-label long-term follow-up study was reported (101), with the patients from the double-blind study previously published by Whitcomb et al (92). In these two latter studies (92, 101), results of operated patients are reported together with non-operated patients with chronic pancreatitis, but the study from Seiler et al only addresses operated patients (103), which also includes data from open-label PERT administration for 1 year.

Compared to placebo, PERT with pancreatin in form of enteric-coated minimicrospheres is associated with a significant improvement of fat (CFA) (92, 103) and protein digestion (coefficient of nitrogen absorption) (103) in patients after pancreatic resection for chronic pancreatitis or pancreatic cancer. In addition, PERT is associated with a significant weight gain and reduced stool frequency (101, 103).

No study has been published which specifically focused on dietary advice for patients after pancreatic surgery, it seems reasonable that a normal healthy diet should be generally recommended if tolerated.

No study has been found to answer the question about the follow-up of EPI in patients after pancreatic surgery. In our opinion, follow-up should be based on symptoms and nutritional evaluation, including body weight and some routine nutritional parameters in blood (e.g. albumin, fat-soluble vitamins). Frequency of visits should be defined depending on the clinical and nutritional status of patients. Once the therapy has been optimised and the clinical and nutritional evaluation is normal, further follow-up should probably be on-demand.

**Question 10**

**What is the Quality of Life (QoL) in operated patients with EPI?**

**Statement**

Pancreatic surgery worsens QoL and exocrine pancreatic insufficiency is a relevant prognostic factor related to impaired QoL.

**Strength of the recommendation and quality of evidence: 1B Strong**

**agreement (A: 72.5%; B: 25%; C: 2.5%)**

**Remarks**

QoL of patients suffering a pancreatic disease is impaired compared to the normative population (104-107). There is also an expected decrease in QoL due to surgery: the early postoperative period is influenced by the type and extent of surgery, and the development of postoperative endocrine and exocrine pancreatic insufficiencies are relevant prognostic factors, significantly affecting the postoperative QoL (40).

Patients undergoing surgery due to pancreatic cancer with EPI score lower on QoL and functional scores (4). Long-term follow-up survivors are generally satisfied with their QoL, but bowel function, steatorrhea, need for treatment of diarrhoea, or need for PERT and food intolerance may impair QoL (108-110). Patients with benign pancreatic tumours had higher QoL values at all time points compared to patients with pancreatitis and cancer. However, it is interesting to point out that QoL in this group did not reach normal values for the healthy population even late after surgery, although these patients underwent curative therapy and did not suffer *per se* a chronic pancreatic disease (40). This is probably due to a higher rate of postoperative EPI (40, 111).

Total pancreatectomy (TP) has a deep influence on short- and long-term changes in the QoL and diabetes mellitus appears to be the most important factor (40, 112); in addition, diabetes has been recently confirmed as the main factor able to have a negative impact on leisure and physical activities, the impact on other life domains being minimal and comparable regardless of whether diabetes resulted from a partial or total pancreatectomy (113).

In acute pancreatitis, patients with long-term survival after surgical treatment for infected pancreatic necrosis have a QoL comparable to that of the normal population. The parameters relevant to rehabilitation and return to normal life such as physical functioning and disease-related disorders (78.5% and 84%), together with general QoL (86%) are statistically the same as those of healthy people (15).

In patients with chronic pancreatitis requiring surgery, QoL improves significantly both in the

short and long term (40). In the study of Izbicki et al(114) global quality-of-life index increased by 67%. Although the number of patients with endocrine and/or exocrine insufficiency is very high in CP, in some studies such complications do not seem to have relevance in the overall reported QoL (22, 27, 115). Regarding the different types of pancreatic head resection, the majority of functional and symptom scales revealed a better QoL and less steatorrhea in duodenum-preserving pancreatic head resection (35, 116).

**CONCLUSION**

Pancreatic surgery is still a great challenge since it is frequently associated with immediate surgical complications as well as long-term sequelae. EPI is a frequent but under-recognized and under-treated complication of pancreatic surgery. The lack of awareness and information regarding the frequency, diagnostic methods and recommended therapy prompted the Spanish Association of Pancreatology to design the present systematic review. EPI is commonly observed after pancreatic surgery, it is clinically relevant and affects QoL; thus it should be investigated, treated and followed-up appropriately. The most important limitation of the literature and the origin of much of the confusion on this topic is that the diagnosis of EPI depends on the definition and the method used for measuring EPI and there is a lack of studies trying to validate PFT with a proper gold standard in operated patients. Therefore further research is needed to look for better and simpler diagnostic tools.

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Table 1

## Table 1. Grading recommendations

| Grade of Recommendation | Clarity of risk/benefit | Quality of supporting evidence | Implications |
|---|---|---|---|
| **1A.**<br><br>Strong recommendation, high quality evidence | Benefits clearly outweigh risk and burdens, or vice versa. | Consistent evidence from well performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. | Strong recommendations, can apply to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present. |
| **1B.**<br><br>Strong recommendation, moderate quality evidence | Benefits clearly outweigh risk and burdens, or vice versa. | Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate. | Strong recommendation and applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present. |
| **1C.**<br><br>Strong recommendation, low quality evidence | Benefits appear to outweigh risk and burdens, or vice versa. | Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain. | Strong recommendation, and applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality. |
| **2A.**<br><br>Weak recommendation, high quality evidence | Benefits closely balanced with risks and burdens. | Consistent evidence from well performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. | Weak recommendation, best action may differ depending on circumstances or patients or societal values. |

| | | | |
|---|---|---|---|
| **2B**.<br><br>Weak recommendation, moderate quality evidence | Benefits closely balanced with risks and burdens, some uncertainly in the estimates of benefits, risks and burdens. | Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate. | Weak recommendation, alternative approaches likely to be better for some patients under some circumstances. |
| **2C.**<br><br>Weak recommendation, low quality evidence | Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens. | Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain. | Very weak recommendation; other alternatives may be equally reasonable. |

From: http://www.uptodate.com/home/grading-guide

Table 2

**TABLE 2. Variability in Exocrine Pancreatic Insufficiency after pancreatoduodenectomy according to the different methods used for measuring EPI**

| **Method** | **EPI %** | **References** |
|---|---|---|
| Coefficient of fat absorption | 55 % | (4) |
| Faecal fat excretion | 87.5 %, 94% | (48, 59) |
| $^{13}$C-labelled mixed triglyceride breath test | 64 %, 62.3%, 51 % | (6, 51, 64) |
| Urinary PABA excretion rate | 33%, 75% | (60, 62) |
| Faecal elastase 1 | 91%, 59%, 87.5%, 50%, 74.5%, 100%, 94.5%, 97.5%, 100 % | (5, 46-48, 54, 55, 57-59) |
| Faecal chymotrypsin levels | 24%, 33% | (50, 52) |
| Clinical steatorrhea | 52.8%, 52.4%, 42%, 64.5% | (49, 53, 56, 63) |