

Consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines

Mary E Phillips ,¹ Andrew D Hopper,² John S Leeds ,³ Keith J Roberts ,⁴ Laura McGeeney,⁵ Sinead N Duggan,⁶ Rajesh Kumar⁷

To cite: Phillips ME, Hopper AD, Leeds JS, *et al.* Consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines. *BMJ Open Gastro* 2021;**8**:e000643. doi:10.1136/bmjgast-2021-000643

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bmjgast-2021-000643>).

Received 9 March 2021
Accepted 8 May 2021

ABSTRACT

Introduction Pancreatic exocrine insufficiency is a finding in many conditions, predominantly affecting those with chronic pancreatitis, pancreatic cancer and acute necrotising pancreatitis. Patients with pancreatic exocrine insufficiency can experience gastrointestinal symptoms, maldigestion, malnutrition and adverse effects on quality of life and even survival.

There is a need for readily accessible, pragmatic advice for healthcare professionals on the management of pancreatic exocrine insufficiency.

Methods and analysis A review of the literature was conducted by a multidisciplinary panel of experts in pancreatology, and recommendations for clinical practice were produced and the strength of the evidence graded. Consensus voting by 48 pancreatic specialists from across the UK took place at the 2019 Annual Meeting of the Pancreatic Society of Great Britain and Ireland annual scientific meeting.

Results Recommendations for clinical practice in the diagnosis, initial management, patient education and long term follow up were developed. All recommendations achieved over 85% consensus and are included within these comprehensive guidelines.

INTRODUCTION

Failure of the exocrine pancreas, referred to as pancreatic exocrine insufficiency (PEI), results in malnutrition, due to malabsorption of nutrients,^{1 2} the catabolic effects of the underlying pancreatic pathology and the impact of the disease on oral intake.³

Clinically, patients with PEI can present with non-specific gastrointestinal (GI) symptoms reflecting maldigestion, including steatorrhoea, weight loss, diarrhoea, abdominal pain and bloating.⁴ Consequently, patients may experience symptoms for prolonged periods before PEI is diagnosed.⁵

It is increasingly recognised that PEI adversely affects survival.^{6 7} Pancreatic enzyme replacement therapy (PERT) is the cornerstone of treatment and is associated

with improved survival and quality of life (QoL) in patients with PEI.^{8–10}

PEI may be underdiagnosed and undertreated in the UK, as demonstrated in other European countries.¹¹ Patient support groups report management of PEI as the most common concern raised on their patient helpline (Pancreatic Cancer UK, 2015), and ‘difficulty in managing GI problems, diet and digestion’ are documented as the primary unmet need in patients with pancreatic cancer (PC).¹² In addition, patients with chronic pancreatitis (CP) feel unsupported by healthcare professionals (HCPs) in the management of PEI (Pancreatitis Supporters Network, 2015). Consequently, there is a need for readily accessible, pragmatic advice for both specialist and non-specialist HCPs. The aim of this article is to provide evidence-based guidance on the diagnosis and management of PEI, including differential diagnosis and follow-up. This article does not make detailed recommendations regarding the management of cystic fibrosis (CF) as this is covered in depth in other guidelines and is outside the clinical expertise of the authors.

METHODOLOGY

PubMed literature searches were performed using the following core key words for each search: PERT OR pancreatin OR pancreatic exocrine insufficiency OR exocrine pancreatic insufficiency OR pancreas insufficiency OR pancreatic insufficiency. For each section topic, additional specific search terms were used (online supplemental table S1). English-language publications describing randomised controlled trials (RCTs), meta-analyses and observational studies were eligible for inclusion (cut-off date 22 May 2020; see online supplemental material). The review of the literature also identified other relevant articles, which were added if



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Mary E Phillips;
mary.phillips1@nhs.net



they met the inclusion criteria. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system¹³ was used to grade the strength of the recommendations (1=strong, 2=weak) and the quality of evidence (A=high, B=moderate, C=low). A consensus on the statements and GRADE scores was obtained from a voting panel of 48 pancreatic specialists, which included leading gastroenterologists, pancreatic surgeons, specialist dietitians, nurse specialists and research clinicians attending the 2019 Annual Meeting of the Pancreatic Society of Great Britain and Ireland annual scientific meeting). Statement 1.2 was added as a result of discussion within this meeting, and therefore was not subject to consensus voting.

RESULTS

Definition and diagnosis of PEI

Statement 1.1: PEI is defined as a reduction of pancreatic exocrine activity in the intestine at a level that prevents normal digestion (grade 1C; 100% agreement)

There is now agreement across pancreatic societies, globally, for this definition.^{14 15} The most common cause of PEI is CP due to loss of functioning pancreatic parenchyma and reduced secretion. Although PEI due to loss of functioning pancreatic parenchyma is also the result of pancreatic cancer, pancreatic resections and CF, other mechanisms exist. Decreased secretion can result from duct obstruction (eg, in periampullary tumour), or secondary causes, such as reduced endogenous stimulation (eg, in small bowel inflammation) and postprandial asynchrony (eg, after gastric surgery).¹⁶

Statement 1.2: Although the coefficient of fat absorption is regarded as the gold-standard diagnostic test for PEI, we recommend that the faecal pancreatic elastase (FEL-1) test is a suitable first-line test for PEI (grade 1B) (note this was not submitted for consensus voting)

Comments

A number of tests have been used for the diagnosis of PEI, including the coefficient of fat absorption (CFA), direct pancreatic function test (PFT), indirect ¹³C-labelled mixed triglyceride breath test and secretin injection at magnetic resonance cholangiopancreatography (sMRCP).^{17 18} These tests are not used in routine clinical practice in the UK,¹⁹ although some, particularly the CFA and direct PFT, are used in controlled clinical studies.¹⁸

FEL-1 is used in clinical practice as it is less invasive and readily available. FEL-1 is a measurement of a pancreatic exocrine-specific enzyme that is not degraded in the bowel lumen, is concentrated during intestinal passage and reflects the total overall pancreatic secretion. FEL-1 testing requires a small amount of faeces²⁰ and is stable at room temperature for 3 days.²¹ A FEL-1 result of <200 µg/g stool suggests moderate PEI, while <100 µg/g suggests severe PEI. The sensitivity of an FEL-1 level of <200 µg/g for PEI, when tested in patients with known risk factors, has been shown to be 25%–65% in mild PEI;

33%–100% in moderate PEI and 82%–100% in severe PEI. The specificity of an FEL-1 level of <200 µg/g has been shown to be 55%–100% (although 6 out of 7 studies show specificity >90%).^{21–28}

Statement 1.3: Stool samples for FEL-1 tests should undergo adjustment to standardised water content, when possible. A repeat test should be considered when a watery sample is reported by the laboratory, or when no definite cause of PEI is identified, to ensure correct diagnosis (grade 2B; 92% agreement)

False-positive results occur when water contaminates a specimen, such as in diarrhoea as samples can become diluted.²⁹ If watery diarrhoea is reported, discussion with the laboratory is advised to ensure adjustment to a standard water content; one study showed that lyophilisation to a standardised water content of 75% was successful.²⁹ If the cause of PEI is still not identified after further investigation and pancreatic imaging, stool testing should be repeated. As FEL-1 only tests for human elastase, the result is unaffected if the patient is taking PERT.²¹ The FEL-1 tests available in the UK were historically monoclonal,³⁰ although more recently, polyclonal tests have become available and have been shown to have equal performance to the FEL-1 monoclonal tests.³¹

Statement 1.4: Positive markers of malnutrition, including clinical history, anthropometric measurements or serum micronutrient levels including magnesium, vitamin E and retinol-binding protein/vitamin A, can be used to support a diagnosis of PEI, if unclear. However, none of these markers should be considered in isolation when diagnosing PEI (grade 2A; 97% agreement)

A patient presenting with suspected malnutrition can be assessed in a number of ways. Initially, this should be conducted clinically by percentage weight loss; however, there is no agreed diagnostic percentage for PEI,^{3 32 33} and fluid balance is also important to consider. The Malnutrition Universal Screening Tool, or Nutritional Risk Screening 2002 if in hospital, are available. Although these tools are not specifically designed for PEI, they do have a high inter-rater reliability ($\kappa=0.67$ –1.00) to identify patients that will likely benefit from nutritional support.^{34 35} A single body mass index (BMI) measurement is of limited diagnostic use on its own and can be normal in patients with PEI.^{36 37} BMI should also be interpreted with caution in an obese population.^{1 38} Evidence for recording specific anthropometric measurements is poor or absent for patients with PEI, with limited data in CP.^{1 39} Serial readings are of most use in this setting.

PEI is associated with some deficiencies in fat-soluble vitamins, trace elements and plasma proteins. Low levels of vitamin E have consistently been reported in patients with PEI or steatorrhoea caused by CP or CF.^{40–42} Studies have suggested retinol-binding protein (used as a marker of vitamin A status) may be lower in patients with alcohol-induced CP and steatorrhoea compared with patients with CP alone,⁴¹ although incidence studies in the CP



population have not shown a significant difference between those with PEI and those without.⁴³

Vitamin A deficiency night blindness is reported in case studies in patients with PEI.⁴⁴ However, studies have not found that serum vitamin A deficiency is predictive of PEI.^{41 42 45 46}

One study in patients with CP showed that serum magnesium <2.05 mg/dL was associated with PEI in univariate analysis; however, it only had a positive predictive value for PEI in CP of 0.58 (95% CI 0.39 to 0.75),⁴³ while zinc deficiency has been associated with CP but not PEI specifically.⁴⁷ Vitamin D deficiency has been shown to have a high incidence in CP (53%–66%) but no significant difference when PEI is present.^{1 41 45 48} Given the evidence available, no finding is specific enough to recommend using serum micronutrients alone as a diagnostic marker for PEI.

Statement 1.5: Cross-sectional imaging and an EUS (without secretin) cannot be used as a diagnostic test for PEI but can support its diagnosis and identify a cause. An abdominal CT scan should also be performed when PEI is diagnosed, especially to exclude a neoplastic cause (grade 2B; 94% agreement)

Comments

CT is recommended when investigating a clinical suspicion of CP, PC or other pancreatic disease that may cause PEI and similar symptoms.^{49–51} CT has been shown to differentiate CP from PC in 90.4% of cases and to exclude other aetiologies for pain or weight loss.⁵² Therefore, CT is the investigational tool of choice to exclude a pancreatic tumour as a cause when a diagnosis of PEI is made.⁵³

Morphological changes of CP, including calcification and main pancreatic duct dilatation, can be identified on CT. Pancreatic calcification is a late or severe feature of CP,⁵⁴ with PEI present in 50% of patients with substantial calcification.⁵⁵ However, only 47% of patients with severe PEI and CP were shown to have significant morphological changes, such as atrophy and ductal dilatation on CT, in a study of 109 patients with CP.^{56 57} One study showed that duct dilatation, diagnosed via endoscopic retrograde cholangiopancreatography, has a stronger association with PEI (OR 5.8) than calcification (no effect).⁵² Parenchymal atrophy has been observed in 54% of patients with CP with CT⁵⁸ and on magnetic resonance cholangiopancreatography (MRCP) in 20% of patients with PEI and 5% of patients without PEI in those with pancreatic pain symptoms, so is neither sensitive nor specific for PEI.⁵⁹ In patients with CP undergoing MRCP without secretin, no significant difference in pancreatic duct size was observed between patients with or without PEI.⁶⁰

Endoscopic ultrasound (EUS) can be used to identify very early parenchymal changes in non-calcific CP with a sensitivity of 84% and a specificity of 80%–100%, but a poor negative predictive value of 45% when compared with histology in high-prevalence groups, suggesting that histological changes can be overlooked.^{61–63} A single-centre experience has shown, in two separate studies in patients with CP (n=115 and 128; 30.4% and 37.5% with

PEI, respectively), that both EUS markers and tissue stiffness measurements (strain ratio) show a linear increase in the likelihood of patients with CP having PEI.^{64 65} The probability of PEI, in the presence of calculi in the main pancreatic duct, was 80%, increasing to 82.8% if the main duct was also dilated. A further study comparing EUS findings with sMRCP showed reduced pancreatic function to be present in normal EUS exams and a predictive value of only 50% when six EUS criteria were present in a group with presumed pancreatic pain but an inconclusive or normal CT scan.⁶⁶ Therefore, although radiological evidence of pancreatic morphological abnormalities is supportive of a diagnosis of PEI, further evidence, including maldigestion symptoms, evidence of malabsorption or a positive FEL-1 test, should be sought to confirm a diagnosis of PEI. A summary of key PEI diagnostic criteria is shown in [box 1](#).

Aetiology of PEI

Statement 2.1: PEI is common in patients with CP (grade 2A; 95% agreement). Given the high prevalence of PEI in patients with severe CP, FEL-1 testing is not required and treatment is recommended in symptomatic patients (grade 2B; 95% agreement)

In CP, progressive destruction of the pancreatic tissue results in PEI.¹⁶ Steatorrhoea is a very late symptom that is associated with severe PEI and substantial decompensation, and is proposed to occur when >90%–95% of pancreatic parenchyma or function is lost.^{2 16} However, steatorrhoea was also demonstrated in patients with more than 10% secretory function,² leading to concerns these publications might result in late diagnosis in patients with less severe disease.⁶⁷ In the long-term, morphological changes, and the development of steatorrhoea or other malabsorption features, make PEI highly likely in patients with CP. Alcohol aetiology, pancreatic ductal obstruction, calcification and duration of disease have all been identified as contributing factors.⁶⁸ PEI is reported in 94% of patients within 10 years of CP onset.³⁷ Multivariate analysis has shown an association between increased mortality in CP and the presence of PEI (OR 2.59).⁶ Given the high probability of PEI in this setting, and the observed benefits of PERT, testing with FEL-1 is redundant and treatment with PERT is recommended.

Statement 2.2: PEI can occur following severe AP, especially in those with necrosis, recurrent AP or in the presence of pseudocysts (grade 2B; 100% agreement). Patients with acute necrotising pancreatitis should be routinely started on PERT once they are able to consume oral intake (good practice point (GPP); 92% agreement)

The FEL-1 test has been used to monitor the presence of PEI following AP. PEI prevalence, following severe and mild attacks of AP, has been reported as 60.5% and 55.6%, respectively.⁶⁹ While there is some recovery in exocrine function over time, a meta-analysis of 10 initial and 39 long-term studies in patients with AP showed that PEI occurred at an overall rate of 62%, was higher in patients with severe AP



Box 1 Diagnosis of PEI

PEI is highly likely with high benefit from PERT: no further test required as significant benefit from treatments and the negative predictive value of FEL-1 is not strong enough to prevent starting treatment

- ▶ Head of pancreas cancer
- ▶ Pre-surgery and post-surgery for head of pancreas cancer with or without pylorus preserving operation
- ▶ Total pancreatectomy
- ▶ Steatorrhoea or malabsorption symptoms in patients with CP with dilated pancreatic duct or severe pancreatic calcification
- ▶ Severe necrotising pancreatitis

Patients that require initial investigation with FEL-1

- ▶ GI symptoms of maldigestion in secondary care with or without known associated conditions
- ▶ Maldigestion symptoms: steatorrhoea, weight loss, diarrhoea, abdominal pain or bloating
- ▶ Associated conditions: patients with coeliac disease, IBS-D, HIV, type 1 diabetes and acute severe pancreatitis after initial phase

Following a positive FEL-1 test

- ▶ A positive FEL-1 requires up-to-date cross-sectional imaging to exclude developing obstructive tumour or lesion as the cause
- ▶ If subsequent investigation cannot find a morphological pancreatic cause of PEI, FEL-1 should be repeated even if patient has already started PERT

Perform a full malnutrition assessment with clinical history, and serum markers specifically including magnesium, vitamin E and retinol-binding protein

- ▶ Where FEL-1 is normal in symptomatic patients with or without lower-risk associated condition and suspicion of maldigestion occurring.
- ▶ When FEL-1 is low to provide a baseline for ongoing surveillance of micronutrient status
- ▶ If micronutrient deficiency is demonstrated, other causes of malabsorption should be considered alongside PEI
- ▶ In cases where there is significant weight loss or clinical signs of micronutrient deficiency to provide a basis for treatment

CP, chronic pancreatitis; FEL-1 faecal elastase-1; GI, gastrointestinal; HIV, human immunodeficiency virus; IBS-D, diarrhoea-predominant irritable bowel syndrome; PEI, pancreatic enzyme insufficiency; PERT, pancreatic enzyme replacement therapy

(66%) compared with those with mild AP (46%) ($p=0.001$) and persisted in 35% of patients on long-term follow-up, with a pooled prevalence of 21% and 42% in patients with mild and severe AP.⁷⁰ While PEI was more common in those with necrosis ($p<0.0001$), there was no difference in the prevalence of PEI in patients with $\geq 50\%$ necrosis compared with that in patients with $<50\%$ necrosis ($p=0.172$).⁷⁰ In a long-term follow-up study in patients who took part in an RCT comparing open necrosectomy with a step-up drainage technique at a median follow-up of 86 months (± 11 months), the incidence of PEI was 29% in patients who had a step-up management of their necrosis compared with 56% in patients who underwent an open necrosectomy ($p=0.03$).⁷¹

Clinical judgement should be used when considering the likelihood of PEI in patients following severe AP, rather than

a straightforward 'indicated' or 'not indicated' decision. A patient with almost total necrosis will most likely have PEI, whereas a patient who has recovered from solely oedematous pancreatitis, with no residual structural damage to the gland, may have normal exocrine function (although the prevalence of PEI appears to be 24%, even in this patient group).⁷⁰ Testing after recovery can be helpful to determine whether long-term exocrine function is impaired. Where the clinician is unclear as to the likelihood or severity of PEI, PERT should be started to prevent nutritional compromise, and function tests should be requested.

Statement 2.3: PEI is common in both resectable and unresectable PC and is progressive in nature (grade 2A; 100% agreement). Given the high prevalence of PEI in this patient population, routine FEL-1 testing is not required, and treatment is recommended (grade 2B; 95% agreement)

PC induces a fibrotic reaction with a consequent reduction in exocrine function. Tumours occurring in the pancreatic head can directly obstruct the pancreatic ducts and are associated with PEI.⁷² PEI, gastroduodenal asynchrony and duodenal obstruction, are common in patients with unresectable PC, with PEI affecting 66%–94% of patients at presentation.^{73 74} Furthermore, PEI is progressive in patients with unresectable PC, with an estimated 10% reduction in exocrine function per month.⁷⁴ The implication is clear: if a patient with PC is found to have normal pancreatic function at presentation, it is likely that PEI will subsequently develop. National guidelines advocate routine use of PERT in patients with unresectable PC,⁷⁵ and pancreatic function tests are only needed where the cause of symptoms is unclear. However, despite this recommendation, three prospective randomised studies have reported a limited benefit of PERT in these patients.^{76–78}

Surgery, particularly pancreaticoduodenectomy, is associated with PEI as it physically reduces the volume of the exocrine component of the pancreas and reduces the stimulation of the gland.^{79 80}

In a meta-analysis of 693 patients with PC from nine observational cohort studies, the median prevalence of PEI was 44% before pancreaticoduodenectomy, 20% before distal pancreatectomy and 25%–50% in patients with locally advanced PC.⁸¹

The high prevalence of PEI in patients with PC (before and after surgery) means that little is gained from PEI testing. The benefits to patient survival (see Statement 3.1) and QoL (see Statement 3.2) with PERT, which have been demonstrated in these patients, means that treatment would usually be indicated, regardless of the FEL-1 result.⁷⁵

Less common causes of PEI

Statement 2.4: Patients with diabetes mellitus may have PEI; however, the exact prevalence is not clear. Those with relevant symptoms should be offered PERT and investigated for a pancreatic pathology (grade 2C; 94% agreement)

There are few large studies investigating the prevalence of PEI in patients with diabetes mellitus (DM), but estimates of 26%–57% and 12%–36% have been reported

for patients with type 1 and type 2 DM, respectively.⁸² Low FEL-1 levels have been associated with reduced glycaemic control in patients with DM ($p=0.031$),⁸³ and one study also reported a weak association with reduced BMI.⁸⁴ Another study reported a negative correlation between FEL-1 level and duration of DM.⁸³ These findings further support the concept that PEI may be a complication of DM.

One study in patients with DM and low FEL-1 (defined as $<100 \mu\text{g/g}$) showed that PERT reduced the frequency of episodes of hypoglycaemia.⁸⁵ This study, however, included few patients with symptoms that would have been compatible with PEI.

Despite a high prevalence of PEI in patients with DM, the identification of individuals who would benefit from PERT, and the potential long-term effects on important

diabetes-related outcomes, requires further investigation as PEI should be considered a symptom of a disease rather than a disease in its own right.

New onset diabetes in the absence of typical risk factors should be investigated as this may be the first sign of pancreatic cancer or CP.⁸⁶

Statement 2.5: PEI should be considered in patients with symptoms of maldigestion in the absence of severe pancreatic disease. In these cases, FEL-1 testing should be undertaken (grade 2B; 100% agreement)

FEL-1 has been successfully used as a case-finding tool for PEI in a minority of patients with coeliac disease, Type 1 DM, HIV, diarrhoea-predominant irritable bowel syndrome (IBS-D) and difficult symptoms after bariatric surgery (table 1). FEL-1 levels $<200 \mu\text{g/g}$ stool have

Table 1 Prevalence of PEI, potential value of PERT and recommendations for less common causes of PEI

Condition	Prevalence of abnormal FEL-1	Benefit of pancreatic enzyme supplementation	Recommendation
DM ^{83 84 158 162–164}	Type 1: 26%–44% Type 2: 12%–20%	One RCT showing reduction in frequency of hypoglycaemia	Statement 2.4: Patients with DM may have PEI; however, the exact prevalence is not clear. Those with relevant symptoms should be offered PERT and investigated for a pancreatic pathology (grade 2C; 94% agreement)
Elderly populations ^{87 165 166}	11.5%–20% in patients 50–80 years of age 1.5% in patients over 90 years of age	No treatment studies reported	Statement 2.5.1: Ageing populations may have an increased prevalence of PEI and, therefore, should be considered for testing, particularly if presenting with unexplained weight loss or diarrhoea (GPP; 88% agreement)
Advanced renal disease ^{167 168}	10%–48%	No treatment studies reported	Statement 2.5.2: Patients with renal disease and rheumatological conditions may have an increased prevalence of PEI but further studies are needed before routine testing can be recommended (GPP; 95% agreement)
Sjögren's syndrome ¹⁶⁹	4% in secondary Sicca syndrome	No treatment studies reported	Statement 2.5.3: Patients with coeliac disease on a gluten-free diet, but still experiencing diarrhoeal symptoms, should be investigated for PEI and treated with PERT if positive results are obtained. This should be reviewed at least annually as treatment may not need to be long term (grade 1B; 100% agreement)
Coeliac disease ^{170–172}	Around 30% with diarrhoea	One RCT showing benefit for 3 months after diagnosis. One open-label study showing benefit in those with persistent diarrhoea	Statement 2.5.4: PEI should be considered in patients with IBS-D. The role of PERT in this group is not fully understood (grade 2C; 95% agreement)
IBS-D ^{103 104}	6.1%–8.6%	One open-label study showing improved pain, stool frequency and consistency	Statement 2.5.5: Patients with inflammatory bowel disease and continued diarrhoeal symptoms should be investigated for PEI (grade 2B; 100% agreement)
IBD ^{173 174}	19%–30%	No treatment studies reported	Statement 2.5.6: Patients with HIV presenting with steatorrhoea, diarrhoea or weight loss should be investigated for PEI and offered PERT if positive results are obtained (grade 2B; 88% agreement)
HIV ^{175 176}	23%–54%	Open-label studies showing improvement in diarrhoea and fat malabsorption	Statement 2.5.7: There may be an increased prevalence of PEI in patients with alcohol-related liver disease but the role of PERT in this group has not been examined (GPP; 89% agreement)
Alcohol-related liver disease ^{177–180}	7%–20%	No treatment studies reported	No statement
Somatostatin analogues ¹⁸¹	24% after a median of 2.9 months of therapy	No treatment studies reported	No statement

See online supplemental material for more detail.

FEL-1 faecal elastase-1; DM, diabetes mellitus; GPP, good practice point; IBD, inflammatory bowel disease; IBS-D, diarrhoea-predominant irritable bowel syndrome; PEI, pancreatic enzyme insufficiency; PERT, pancreatic enzyme replacement therapy; RCT, randomised controlled trial.

been reported in 11.5%–13.1% of patients presenting to secondary care clinics, and a separate study demonstrated that 79.6% of patients with low FEL-1 responded to PERT,^{87 88} indicating that they have PEI. Follow-up data are required to ascertain how many of these patients developed pancreatic pathology.

Recommendations for other, less common, causes of PEI, such as coeliac disease, HIV, IBS-D and alcohol-related liver disease, are shown in [table 1](#), and detailed supporting evidence is shown in the online supplemental material.

The value of PERT

Statement 3.1: PERT is associated with improved survival in patients with CP (grade 1C) and PC (grade 2B). Additionally, PERT is associated with improved nutritional status in patients with CP (grade 1C) and PC (grade 1C) (95% agreement)

PERT has been shown to improve symptoms and digestion in patients with pancreatitis.⁸⁹ In patients with AP, PERT maintained global health status.⁹⁰ Among patients with CP, PERT has been shown to improve fat and nitrogen absorption, nutritional parameters and GI symptoms.⁹¹

PEI has been shown to be an independent factor related to mortality in patients with CP,⁶ and an absence of PERT on discharge was an independent risk factor for survival in those undergoing surgery for CP.⁹²

In a small, randomised trial conducted over an 8-week period in 21 patients with unresectable PC, those receiving PERT maintained body weight (gain 1.2%; 0.7 kg), while patients without PERT lost body weight (loss 3.7%; 2.2 kg) (both $p=0.02$). CFA increased by 12% in the PERT group and declined by 8% in the control group, but this difference did not reach statistical significance ($p=0.13$).⁷⁷ An RCT in Korea failed to observe any benefit of PERT on body weight ($p=0.381$), subjective global assessment ($p=0.18$) or survival ($p=0.744$) compared with placebo over an 8-week period in 67 patients with unresectable PC.⁷⁶ It should be noted that patients were not permitted to receive H₂-receptor antagonists or proton-pump inhibitors (PPIs) and, consequently, PERT may not have been effective without adequate neutralisation of gastric acid. The dose of PERT was also quite low at 2×25 000 units of lipase three times daily with main meals and one capsule with snacks. In addition, only 43% of patients included had severe PEI (FEL-1 level <100 µg/g stool), and only a third having tumours in the pancreatic head (35.5% in the PERT group; 33.3% in the placebo group). Furthermore, although the difference was not statistically significant, more patients in the PERT group had a FEL-1 level ≥200 µg/g than those in the placebo group (44.1% vs 21.2%; $p=0.13$). Hence, this trial has several limitations, and the results should be interpreted accordingly.

Further work in exploring the potential benefits of PERT on survival identified a link between the severity of PEI and reduced survival in a non-randomised study of 194 patients with PC. A FEL-1 level ≤20 µg/g was an independent predictor of survival (HR 1.59; $p=0.023$).⁷

Treatment with PERT appeared to improve survival in a recent Spanish retrospective single-centre study.⁹ Patients ($n=160$) with unresectable PC were treated by different teams who either prescribed high-dose PERT, if needed, or did not. Median survival was significantly longer among patients managed by the team more likely to prescribe PERT (189 days; 95% CI 167.0 to 211.0 days *vs* 95.0 days; 95% CI 75.4 to 114.6 days) (HR 2.12; 95% CI 1.49 to 3.00; $p<0.001$). However, the results should be interpreted with caution due to potential selection bias arising from the retrospective non-randomised study design. In a retrospective study of 469 patients who had undergone resection of periampullary cancer, PERT was associated with a median increase in survival on both multivariate ($p=0.044$) and propensity-matched analyses ($p=0.009$). Survival benefit was most markedly observed among patients treated with PERT and with pancreatic duct widths of ≥3 mm (HR 0.64; 95% CI 0.47 to 0.89; $p=0.006$).⁸

A retrospective, population-based, propensity-matched, observational study in the UK matched 1614 patients with PC who did or did not receive PERT.⁸ The adjusted median survival time was 262% longer among PERT-treated patients compared with matched, non-PERT-treated controls (survival time ratio 2.62; 95% CI 2.27 to 3.02). This survival benefit was present in patients who did not receive chemotherapy or surgery, suggesting that this benefit was independent of other interventions.

Overall, there are conflicting data regarding PERT and survival, with RCTs limited by heterogeneous populations and other data limited by retrospective or observational trial design. More robust studies are required to strengthen this recommendation.

Importantly, a large survey of 208 patients with PC who were prescribed PERT in the USA identified that only 89 patients (66% of those prescribed PERT correctly), were taking their enzymes as instructed. Predominantly, this was due to incorrect prescriptions, with 35% of patients not prescribed PERT with meals and snacks. Patients who were taking their enzymes with meals, rather than before or afterwards, were more likely to gain weight ($p=0.022$) and demonstrate less maldigestion ($p=0.003$) and less steatorrhoea ($p=0.04$) compared with those not taking PERT correctly.⁹³ The high incidence of incorrect timing is an important consideration when analysing data from studies assessing the clinical response to PERT, especially when data are collected retrospectively.

Statement 3.2: Treatment with PERT improves QoL in patients with PEI (grade 1C; 100% agreement)

While PERT is useful for treating PEI, studies that address whether it has a positive effect on the QoL of those taking it have been of variable quality. Achieving equipoise, and assessment over an appropriate time period, can affect study design and interpretation, especially in the PC cohort.

Being able to justify the pill burden associated with PERT by confirming an associated improvement in QoL is both relevant and important. While initiating PERT

often requires specialist input, there is an ongoing need for patient self-management of PERT dosing. A small qualitative trial explored patient experiences, recruiting patients who were receiving PERT for at least 6 months following pancreaticoduodenectomy for malignancy. Patients reported concerns over the use of PERT at social events, difficulties in remembering to take treatment and struggles with dose adjustment. Socially debilitating symptoms of PEI (excessive flatulence and steatorrhea), and the importance of PERT, were also acknowledged. The authors concluded that education and access to specialist support was important to patients.⁹⁴

Two cohorts of patients with PEI, secondary to CP, were observed over a 1-year period, with assessment at 6 months and 1 year. Assessment of symptoms and QoL in patients already receiving PERT (n=206) and in patients starting treatment with PERT (n=88) were compared. PERT dosing was not controlled by the study design. Data from 294 patients were analysed; 256 patients completed the validated Gastrointestinal Quality of Life index (GIQLI). GIQLI scores in the untreated were significantly lower than those on treatment at baseline ($p < 0.001$), but this difference disappeared after 6 months of treatment. The mean total GIQLI score improved significantly over 1 year for the study population ($p < 0.001$), as did all five subscores (symptoms scale, physical function, social function, emotion and medical treatment). Overall, both cohorts exhibited significant improvements in QoL (both $p < 0.001$), suggesting that improvement in QoL may be sustained with continued PERT.¹⁰

Another prospective study examined the effect of PERT versus placebo on QoL in patients with moderate-to-severe AP, using the Clinical Global Impression of Disease Symptoms (CGIDS) tool alongside version 4 of the validated Functional Assessment of Cancer Therapy-Pancreas QoL questionnaire.⁹⁰ Recruitment issues led to termination of the study with 56 patients enrolled, but over the 26–30 day study period, there was an improvement in the CGIDS scores with numerically, but not statistically significant worse flatulence in the placebo group ($p = 0.503$). Of note, was a FEL-1 level $< 200 \mu\text{g/g}$ in only 20 patients. The QoL assessment also favoured the PERT group, but only the 'emotional well-being' score, demonstrated a significant improvement in the PERT group versus placebo ($p = 0.04$).⁹⁰

More recently, work has been undertaken to develop a tool to identify patient-reported outcome measures in patients with CP (n=91). This tool correlated well with GIQLI scores, and patient scores correlated with disease severity ($p < 0.0001$). It could be used in future research to provide a less invasive measure of treatment effect.⁹⁵

In summary, there are data supporting the use of PERT to improve QoL in patients with AP, CP and resectable and non-resectable PC, but further high-quality studies are required.

Management of PEI

Statement 4.1: Patients should consent for the porcine nature of PERT (GPP; 97% agreement)

All currently available PERT preparations are porcine (a non-porcine PERT formulation was in development, but it failed to meet its primary endpoint in a phase III clinical trial).⁹⁶ Patients should be made aware of the porcine origin of PERT before commencing therapy. Jewish and Muslim faith leaders consent to the use of PERT as there are no alternatives available.⁹⁷

Statement 4.2: PERT should be started at a dose of at least 50 000 units lipase with meals and 25 000 units lipase with snacks (grade 1A), and patients should be encouraged to adjust their dose if this is ineffective (grade 2C) (92% agreement)

The choice of PERT preparation needs to consider the lipase units the patient requires and the number and size of capsules the patient is able to swallow. Studies support the use of at least 50 000 units lipase as a suitable starting dose with meals and 25 000 units lipase with snacks.^{91 98} All guidelines endorse dose escalation if the initial dose is not effective.^{77 99 100}

Statement 4.3: Consumption of pancreatic enzymes should be spread out throughout a meal (grade 1C; 100% agreement)

A study examining the timing of PERT in 24 patients with CP suggested that spreading the dose throughout the meal supported optimal absorption.¹⁰¹ However, this trial was limited by strict exclusion criteria: no pancreatic or GI surgery, no antacid therapy, no gastro paresis, no excessive alcohol intake or malignancy, no opiate prescription and the use of a prokinetic prior to the test.¹⁰¹ These data were supported by a survey of 262 patients, which demonstrated that patients consuming PERT throughout meals experienced fewer abdominal symptoms and more weight gain compared with patients who consumed PERT before or after meals.⁹³

Statement 4.4: If capsules cannot be swallowed, they should be opened, placed on an acidic puree and swallowed at intervals throughout the meal, and the mouth should be rinsed with cool water to prevent ulceration (GPP; 97% agreement)

Some patients are unable to swallow capsules. In those circumstances, the capsules can be opened and the contents taken on a spoonful of cold acidic food, such as fruit puree, apple sauce, jam or fruit yoghurt and swallowed immediately.

This should then be washed down with a cool or room-temperature drink to ensure that no granules remain in the mouth, where they could cause ulceration. Special care should be taken by those who wear dentures. Granules should not be chewed or crushed as this removes the enteric coating, resulting in premature activation of the enzymes.

Statement 4.5: There is no maximum dose of PERT in adults (GPP); however, where doses exceed 100,000 units lipase with meals, comorbidities should be excluded (GPP; 91% agreement)

The most frequently documented side effects of PERT are nausea, vomiting and abdominal discomfort. Further details of rarer side effects can be found in Statement 7.1.

The product itself does not raise toxicity concerns in the event of unnecessary or excess treatment. However, pill burden should be considered, and when dose escalation has not resolved ongoing symptoms, comorbidities should be considered (see Statement 5.1).

Statement 4.6: Dietary fat restriction is not routinely recommended, but very high-fibre diets should be avoided (grade 1C; 96% agreement)

Some patients require a high-fat, high-protein diet if they are nutritionally depleted and have a low appetite. Increasing the fat content of the diet has been shown to be well tolerated in patients with CP.^{102 103} Low-fat diets may exacerbate malnutrition and should be avoided, unless there is a specific reason for fat intolerance. Very high-fibre diets (>25 g/day) may absorb enzymes and delay nutrient absorption and, therefore, are not recommended.¹⁰⁴

Statement 4.7: Where needed, enteral feeds should be peptide and medium-chain triglyceride-based (grade 2C; 100% agreement)

One small pilot study examined the use of peptide versus polymeric feeds in patients with severe AP.¹⁰⁵ Nutritional status and biochemical markers were assessed 2 weeks into the study. In populations with severe AP, it is unlikely that any significant change would be observed within this time period. While the study concluded that there was no difference between the two feed types, analysis of the secondary endpoints, including weight loss and length of stay, demonstrated an improvement in the peptide-fed group, suggesting that malabsorption of feed, secondary to PEI, has an impact on recovery.¹⁰⁵ Other guidelines have used extrapolated data from studies comparing enteral and parenteral nutrition to make strong recommendations regarding the use of peptide-based feeds (grade A), but these data support enteral over parenteral nutrition, rather than a specific feed,¹⁰⁶ resulting in conflicting recommendations.¹⁰⁷

Statement 4.8: Both acid (grade 1C) and temperature (GPP) impact the efficacy of PERT. The addition of a PPI can be useful if PERT is not effective (grade 1C, 97% agreement). If one PERT product remains ineffective, despite the use of a PPI, a trial of an alternative PERT preparation is recommended (GPP)

Several studies have shown increased efficacy of PERT with the addition of a PPI, as PERT may be inhibited by gastric acid.^{108–110} However, the data are not consistent, with some studies showing no benefit.^{111 112} Specifically in pancreatic cancer, one study suggests a PPI may help reduce further pancreatic atrophy,¹¹³ but studies are limited by heterogeneous cohorts.^{110 111}

Given the conflicting data, and the potential for long-term complications of PPI use, including *Clostridium difficile* infection, hypomagnesaemia, nausea and diarrhoea,^{114 115} the addition of a PPI is a second-line treatment for the management of PEI.

Optimum storage of enzymes (below 25°C) to prevent deterioration of function during storage is important.^{116–119} Each PERT product functions slightly differently at different pHs and timings,^{120–122} so considering the use of an alternative PERT product may be beneficial, particularly in cases where gastric transit is altered.

Statement 4.9: Patients with PEI receiving enteral feeds usually tolerate semielemental (peptide) preparations. However, where malabsorption symptoms persist, enzymes can be flushed via the feeding tube every 2 hours or added to the feed itself (GPP; 93% agreement)

Semi-elemental (peptide) feeds require less PERT to achieve complete lipolysis than polymeric feeds¹²³; therefore, peptide feeding is recommended for patients with PEI who are receiving enteral feeds. When considering a choice of feed product, it is sensible to consider the total fat content and the proportion of medium-chain and long-chain triglycerides as well as the polysaccharide content. This information, alongside nutritional requirements, fluid needs and tolerance, will assist in the selection of an appropriate feed. Effective mixing of feed with enzymes is difficult to achieve, especially with jejunal feeding, and administration of the enzymes, either as flushes or mixed directly with the feed, has been documented,^{124 125} but evidence is limited, with no safety or stability data available (box 2). Jejunal feeding will, theoretically, reduce stimulation of the pancreas¹²⁶ and

Box 2 Administration of PERT with enteral feeds

Powdered enzymes and feeding tubes

NB. Once mixed, use all products immediately. Do not leave to stand

Giving PERT as flushes: mix 1 g scoop pancreatin powder (Pancrex V Powder, Essential Pharmaceuticals, UK) with 50 mL sterile water. Shake well and immediately flush via a feeding tube. Do not give with other medication. Do not flush between the feed and the enzyme as this will reduce the mixing of the feed with the PERT. Administer every 2 hours throughout enteral feeding, increase dose of PERT if needed.

Mixing PERT with feed: add 1–2 g Pancrex V Powder directly to the feed in a feeding reservoir. Shake well. Hang straight away and for 4 hours only, increase dose of PERT if needed. (NB. Some feeds congeal when PERT is added - discuss with a tertiary centre dietitian prior to adding PERT to feed)

Flushing granules/mini-microspheres via large bore tubes (>CH20): mix with an acidic juice (such as Forti Juice (Nutricia Clinical Care, UK); Ensure Plus Juice (Abbott Nutrition, UK); Fresubin Jucy Drink (Fresenius Kabi, UK)) and flush via the feeding tube every 2 hours throughout enteral feeding, increase dose of PERT if needed

PERT, pancreatic enzyme replacement therapy

Table 2 Evaluation of the need for PERT dose escalation: nutritional and symptom assessments

Anthropometric	Biochemical	Clinical	Dietary
<ul style="list-style-type: none"> ▶ Weight changes in relation to nutritional intake (unexplained weight loss / failure to gain weight) ▶ Functional changes (grip strength, sit-to-stand times, 6 min walk) 	<ul style="list-style-type: none"> ▶ Micronutrient status (iron, ferritin, B₁₂ and folate, fat-soluble vitamins, selenium, zinc, magnesium, copper, clotting) ▶ Glycaemic control (HbA1c and random glucose) ▶ Inflammatory markers for assessment of accuracy of micronutrients (CRP) 	<ul style="list-style-type: none"> ▶ Stool frequency, texture, colour, appearance, presence of oil, floating/difficult to flush, ▶ Flatulence, bloating, abdominal pain ▶ Medication that may mask symptoms (opioids, ondansetron, iron supplements, etc) 	<ul style="list-style-type: none"> ▶ 24-hour dietary recall with relevant PERT dose to assess adherence and ratio of PERT with nutrition ▶ Food avoidance due to abdominal symptoms ▶ Avoidance of fat-containing products ▶ Nutritional adequacy of diet

CRP, C reactive protein; HbA1c, haemoglobin A1c; PERT, pancreatic enzyme replacement therapy.

may mean that patients are more likely to require PERT compared with those receiving gastric feeding.

Statement 4.10: When malabsorption has been corrected, nutritional status and bowel symptoms should improve; thus, monitoring of these symptoms should support ongoing treatment or dose escalation (GPP; 95% agreement)

To assess the need for PERT dose escalation, nutritional and symptom assessments can be used as summarised in [table 2](#).

Differential diagnosis/treatment failures

Statement 5.1: When symptoms continue, despite treatment with pancreatic enzymes, clinicians should ensure that PERT products are being taken correctly, the dose has been adequately escalated and other conditions have been excluded (GPP; 100% agreement)

Treatment with PERT does not completely normalise digestion, and undertreatment is common, with many patients continuing to experience symptoms of malabsorption, placing them at risk of nutritional deficiencies. A study in Germany showed significant improvement in GI symptoms, pain and QoL in both newly diagnosed patients and those with established CP, following review of PERT ($p < 0.001$), demonstrating the benefit of dose review.¹⁰

No treatment is 100% effective, but the steps in [box 3](#) should help to optimise management of PEI. If symptoms of PEI continue, despite optimising PERT dose, then other causes should be considered. Small bowel bacterial overgrowth (SBBO) was reported in 36% of patients with CP in a meta-analysis of nine studies.¹²⁷

Bile acid diarrhoea, sometimes referred to as bile acid malabsorption (BAM) should also be considered; however, while the prevalence of this condition in patients with PEI is unknown, many patients with pancreatic disease have undergone cholecystectomy as part of the management of gallstone disease,¹²⁸ which is associated with a risk of BAM.^{129 130}

Two studies have shown an increased prevalence of PEI in patients with IBS-D,^{131 132} but the prevalence of functional symptoms in patients with exocrine dysfunction is unknown.

In summary, once dose is optimised, ongoing symptoms should be investigated by taking a structured history and performing coeliac serology, investigation for SBBO using a glucose hydrogen breath test, colonoscopy with colonic biopsies and a selenium homocholic acid taurine (SeHCAT) scan. Other causes of ongoing symptoms should be investigated as per the British Society

Box 3 Practical guidance for the management of continued symptoms despite commencement of PERT

Timing and dosing

- ▶ Ensure that the correct dose of enzymes is prescribed; minimum of 50 000 units lipase per meal and 25 000 units lipase per snack. Many patients require more than this for adequate digestion. Escalate the dose and monitor for effect
- ▶ Check PERT is taken appropriately, that is, with all food and milky drinks, spread throughout the meal rather than taking at the start or end of the meal
- ▶ Ensure PERT is being taken with all intake, for example, nutritional supplements, milky drinks, eating outside the home, snacks

Preventing denaturing of the enzyme

- ▶ Check how the PERT is stored (<25°C: avoid storage in direct sunlight, cars, near heat sources such as kettles)
- ▶ Consider gastric acid suppression

Factors affecting interpretation of symptoms

- ▶ Exclude constipation and overflow diarrhoea
- ▶ Check if any other medication that may be causing abdominal symptoms is being taken, for example, laxatives, chemotherapy, metformin, antiemetics

If symptoms are not controlled

- ▶ If symptoms remain despite a dose of $\geq 10\,000$ units lipase/kg/day, then other causes of the symptoms should be considered before increasing the dose of PERT further
- ▶ Other causes of loose stools should be investigated, for example, SBBO, IBD, BAM, infection, coeliac disease, lactase deficiency, other food intolerances (see online supplemental table S2 for further details)

BAM, bile acid malabsorption; IBD, inflammatory bowel disease; PERT, pancreatic enzyme replacement therapy; SBBO, small bowel bacterial overgrowth



of Gastroenterology guidelines for the investigation of chronic diarrhoea in adults.¹³³

Long-term follow-up in patients with PEI

Statement 6.1: Patients with PEI often have ongoing problems with malnutrition, malabsorption and bowel symptoms; therefore, long-term follow-up is recommended (GPP; 100% agreement)

Long-term support is not easily accessible for patients with pancreatic disease in the UK, with a survey of UK practice demonstrating that most patients were not followed up after discharge,¹³⁴ resulting in inconsistent advice, often provided by non-specialists. A lack of guidance on the management of GI symptoms, diet and digestion has been identified as the primary unmet need of both patients and their carers.¹² In benign disease, GI symptoms may have a long-term impact on QoL in those with AP and CP.^{135 136}

Long-term follow-up should address issues with education, the management of PERT and should provide formal provision for long-term monitoring of nutritional markers and micronutrient status.¹³⁷ This nutritional follow-up should include clinical, anthropometric and biochemical measures of nutritional status,^{137 138} and the development of a structured annual assessment (figure 1) could follow the model established for coeliac disease.¹³⁸ Clinicians need to be pragmatic; the assessment of patients with rapidly progressing disease should focus on QoL and management of symptoms, whereas long-term health must be a consideration in those with benign disease or those who have undergone treatment with curative intent (table 3).

Statement 6.2: Based on the literature search, no studies have been published to support a direct association between PEI and bone health. However, there is a high prevalence of osteoporosis and osteopenia in patients with pancreatic diseases that also result in PEI. Therefore, the best practice would be to implement routine monitoring of bone mineral density in pancreatic diseases (GPP; 100% agreement)

Limited data are available to support a conclusive link between PEI and bone health, and no studies were identified from the literature search that investigated a direct association (see details in the online supplemental material).

Min *et al.*¹³⁹ reported that 31/45 (68.9%) patients with CP and PEI had either osteoporosis or osteopenia. A statistically significant association between low FEL-1 and low bone mineral density was reported in patients with PEI and CP, as assessed by X-ray ($p < 0.05$), but not by dual X-ray absorptiometry (DXA)—the latter being the gold standard for assessing bone mineral density.¹⁴⁰ Patients on PERT had higher bone mineral density, as assessed by DXA ($p < 0.05$). In 167 patients with osteoporotic bone fractures, it was found that PEI (low FEL-1) was more frequent compared with non-fracture controls¹⁴¹: 34% of patients with osteoporosis had FEL-1 levels $< 200 \mu\text{g/g}$, and FEL-1 levels were 65% lower in patients than in healthy controls. Furthermore, vitamin D,

parathyroid hormone and calcium levels correlated with FEL-1 level ($p < 0.01$).¹³⁹

Finally, in an uncontrolled study, 13 of 14 patients with CP, all of whom had PEI, had either osteoporosis or osteopenia.¹⁴² No association was identified between osteoporosis/osteopenia and the secretin test or faecal fat excretion.

A systematic review and meta-analysis of the prevalence of osteoporosis and osteopenia in CP identified eleven studies and 10 were included in the meta-analysis: seven articles and three conference proceedings. This meta-analysis of 513 patients found that 23.4% of patients with CP had osteoporosis, 39.8% had osteopenia and 65% had either osteoporosis or osteopenia.¹⁴³ Only one of the studies included in the systematic review by Duggan *et al.* (2014a) was retrieved in the broad literature search for the current systematic review,¹⁴² and none were retrieved following the application of search filters. Of the 11 studies in the Duggan *et al.* (2014a) review, five^{144–148} reported an association between low bone mineral density and low FEL-1, while one study¹⁴⁹ found no such association.

The National Institute for Health and Care Excellence guideline for pancreatitis¹³⁷ recommends bone mineral density assessment, by DXA scan, every 2 years for those with CP.¹³⁷ The HaPanEU guidelines¹⁵⁰ recommend that, as well as regular DXA scanning, all patients with CP should receive basic preventative measures to protect against the deterioration of bone mineral density, including adequate diet (particularly calcium and vitamin D intake), regular weight-bearing exercise and the avoidance of smoking and alcohol. For pancreatic diseases other than CP, given the morbidity and mortality associated with osteoporosis and fracture, as well as the preventable nature of osteoporosis, it seems prudent to recommend routine monitoring of bone mineral density using DXA scans in benign or curative disease.

Adverse events

Statement 7.1: PERT is not associated with any significant complications (grade 1A; 100% agreement)

There are many RCTs examining the efficacy of PERT, and all report safety data for the duration of the trial. Some of these are open-label extensions, up to 12 months, but there is a paucity of RCTs examining the long-term effects of PERT.

Industry-funded studies report mild abdominal pain as an adverse event (AE) in patients with CP (3/34) but no patients withdrew as a result of an AE.¹⁵¹ Whitcomb *et al.* identified 8/25 patients reporting AEs (flatulence, change in bowel habit, increased bowel frequency, hypoglycaemia and hyperglycaemia) in a trial exploring the use of PERT in a mixed cohort of patients with CP, or pancreatic resection, who were taking 72 000 units lipase with meals and 36 000 units lipase with snacks.¹⁵² Interestingly, there were 8/29 AEs of similar nature in the placebo group.

A 6-month open-label extension in 48 patients already established on PERT due to CP or pancreatic surgery found four patients reported AEs potentially associated with treatment: weight gain ($n=1$), abdominal distension

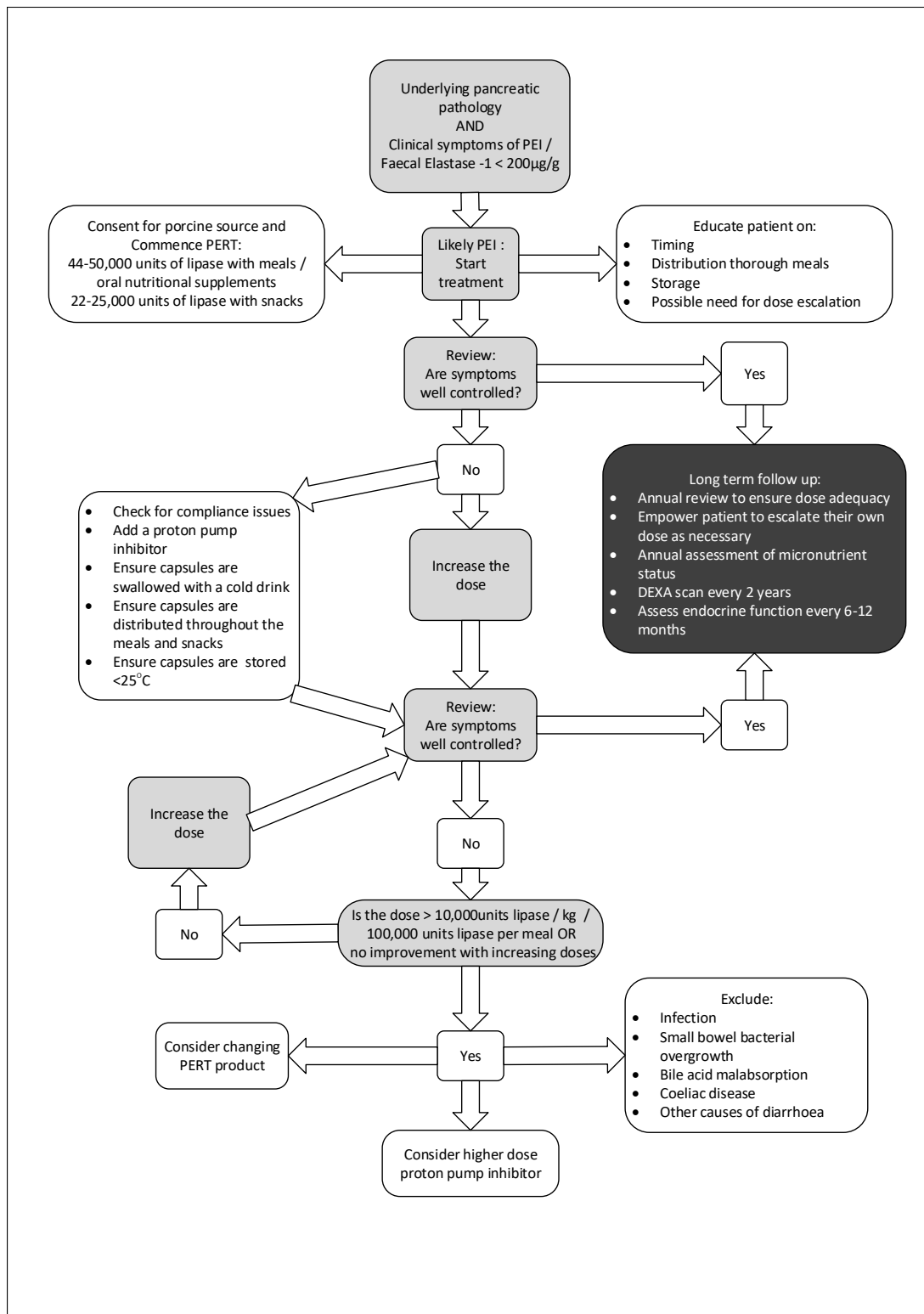


Figure 1 Summary of guidance. DXA, Dual-energy X-ray absorptiometry; PEI, pancreatic enzyme insufficiency; PERT, pancreatic enzyme replacement therapy; PPI, proton-pump inhibitors.

(n=1), flatulence (n=1), abdominal pain (n=1) and diarrhoea (n=1). These were all classified as mild, and there were no withdrawals from the study as a result.¹⁵³

In a cross-over trial using two different PERT products, the total number of AEs across both groups was reported as: headaches (4/46), diarrhoea (2/46), infection (3/46) and

abdominal pain (2/46).⁹⁹ Subsequently with an additional cohort 8/61 patients reporting AEs including constipation, abdominal discomfort and frequent bowel motion.⁹¹

A placebo-controlled study examining the use of PERT in 95 patients with type 1 DM found no difference in the frequency of AEs between the intervention group (40 000

**Table 3** Long-term follow-up recommendations

	Patients with benign disease and those who have undergone curative treatment for malignant disease	Patients undergoing palliative management
Anthropometric and functional assessment	<ul style="list-style-type: none"> ▶ Body weight ▶ Grip strength ▶ Mid-arm muscle circumference as appropriate ▶ CT scans can be assessed for muscle mass if available ▶ 6-min walk tests/sit-to-stand function tests if more detailed functional assessment is required ▶ DXA scans should be carried out every 2 years 	<ul style="list-style-type: none"> ▶ Body weight ▶ Grip strength/mid-arm muscle circumference as appropriate
Clinical	<ul style="list-style-type: none"> ▶ Assessment of bowel symptoms: stool frequency, colour ▶ Presence of abdominal bloating/wind ▶ Postprandial abdominal pain ▶ Factors impacting on QoL ▶ Change in medication (especially opioids and anti-emetic/anti-diarrhoeal medications) ▶ Compliance with treatment ▶ Implementation of lifestyle advice (smoking, alcohol cessation, weight-bearing exercise, sunlight exposure) 	<ul style="list-style-type: none"> ▶ Factors impacting on QoL ▶ Assessment of bowel symptoms: stool frequency/colour ▶ Presence of abdominal bloating/wind ▶ Postprandial abdominal pain ▶ Change in medication (especially opioids and antiemetic/antidiarrhoeal medications) ▶ Compliance with treatment
Biochemical	<ul style="list-style-type: none"> ▶ Vitamin A, D, E ▶ Clotting studies (vitamin K) ▶ Parathyroid hormone ▶ Magnesium ▶ Zinc, copper, selenium ▶ Full blood count and iron studies ▶ Vitamin B₁₂ and folate ▶ ESR/CRP ▶ Glucose and HbA1c 	<ul style="list-style-type: none"> ▶ Full blood count, iron studies, CRP ▶ Glucose and HbA1c

CRP, C reactive protein; DXA, dual X-ray absorptiometry; ESR, erythrocyte sedimentation rate; HbA1c, haemoglobin A1c; QoL, quality of life.

units lipase with meals and 20 000–30 000 units lipase with snacks) and the control group; however, a reduction in mild and moderate hypoglycaemia was observed in the intervention group at the end of the study.⁸⁵ The most common AEs reported were headache, infection, pain, diarrhoea and dyspepsia; the incidence of each AE was not specified, but the overall incidence was the same in both the intervention and placebo groups. Changes in glycaemic control, due to PERT in patients with existing PEI, were only reported as sufficient to cause a change in management in one patient in a cohort of 36 patients with DM as part of a larger study consisting of 54 patients.¹⁵⁴ There was no treatment-related AEs in the non-diabetic group.¹⁵⁴

While these trials are small, they are all consistent in results. Regardless of trials not reporting serious AEs, fibrosing colonopathy (FC) cannot be ignored.

Statement 7.2: There is limited evidence to suggest that long-term use of very high-dose PERT may be associated with fibrosing colonopathy in children with CF, resulting in a dose restriction of 10 000 units lipase/kg/day in this population (grade 1C; 100% agreement)

Comments

Cases of FC were first reported in 1992 and are thought to be associated with high doses of PERT (>19 000 units lipase/kg/day in the initial reports).¹⁵⁵ Causal factors, including the presence of Eudragit L30D-55 acrylic resin within the enteric coating, were debated,¹⁵⁶ but the initial research into this was discredited.¹⁵⁷ Contributing factors were summarised as young age, previous intestinal surgery, meconium ileus and the use of corticosteroids,

deoxyribonuclease and H2 blockers, and all cases were reported in children with CF.^{158–160}

Patients who presented before the formation of strictures were identified as having reversible symptoms that resolved on lowering the dose of PERT, suggesting the risk increased with higher doses. However, following the publication of case reports describing the presentation of FC in neonates who had not received any PERT, the debate over the mechanism behind the development of FC continues.^{160 161} At present, a maximum dose of 10 000 units lipase/kg/day is recommended for children with CF. There is no maximum dose proposed for adults or children with non-CF-related PEI. Recognition features of FC are documented in [table 4](#).

Use in pregnancy and breastfeeding

Statement 8.1: Further work is required to confirm the efficacy and safety of PERT during pregnancy and breastfeeding; although the authors have experience of successful use in pregnancy, the numbers are small and there are no published data. Malabsorption should be avoided in pregnancy (GPP; 93% agreement)

The systematic literature search did not identify any articles concerning the use of PERT in pregnancy or breastfeeding. Essential fatty acids are required for brain and retinol development in the first 8 weeks of gestation.¹⁵⁹ Thus, it is important that adequate PERT is maintained in pregnancy.

Summary

This document serves as an evidence-based guide for the diagnosis and treatment of PEI. Data were derived

Table 4 Symptoms of fibrosing colonopathy

 Symptoms of FC are documented as¹⁸²:

Clinical symptoms	Clinical signs	Imaging characteristics
Failure to thrive, persistent malabsorption despite enzyme therapy	Bloody diarrhoea	Loss of haustrations (sacs formed during colonic movements to facilitate the movement of faeces through the colon), also referred to as a 'lead pipe' colon (appearance of a smooth colonic wall on imaging)
Persistent abdominal pain with obstruction/distension	Chylous ascites	Dilatation of terminal ileum
	Reduced peristalsis	Thickened bowel wall

through a pragmatic review of the literature, and conclusions were assessed by a multidisciplinary panel of experts in pancreatology at the 2019 Annual Meeting of the Pancreatic Society of Great Britain and Ireland.

The strengths of this work are the comprehensive nature of the assessment and the focus on the practical aspects of managing PEI. Also addressed are areas of uncertainty, or areas where practice is difficult or variable, such as diagnostic tests and treatment of patients whose symptoms are vague or refractory to PERT.

Author affiliations

¹Nutrition and Dietetics, Royal Surrey Hospital NHS Foundation Trust, Guildford, UK

²Department of Gastroenterology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

³HPB Unit, Freeman Hospital, Newcastle Upon Tyne, UK

⁴HPB Surgery, Queen Elizabeth Hospital Birmingham, Birmingham, UK

⁵Nutrition and Dietetics, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

⁶Department of Surgery, Trinity College Dublin, Dublin, Ireland

⁷HPB Surgery, Royal Surrey Hospital NHS Foundation Trust, Guildford, UK

Acknowledgements The authors would like to acknowledge the support of Jeremy French and Lynne McCullum in developing the content of this document.

Contributors All authors were involved in the design, writing and reviewing of this document. All authors contributed to the design, analysis and interpretation of data. All authors drafted sections of the paper and critically appraised the entire paper prior to submission.

Funding Editorial assistance was provided by Alphamaxim Healthcare Communications which was funded by Mylan Products Limited. The guideline content is independent of and not influenced by Mylan. Publication fees were met from an academic research account affiliated with Sheffield Teaching Hospitals.

Competing interests MEP has received honoraria for teaching and resource development from Mylan, Nutricia, and Sanofi. AH has received honoraria for teaching and resource development from Mylan. JSL has received honoraria for teaching and consulting from Mylan. KJR has received honoraria for teaching from Mylan and Abbott. LM has received honoraria for teaching and conference attendance from Mylan. SND has received honoraria for teaching, consulting and conference attendance from Mylan and Abbott. RK has received honoraria for teaching from Mylan.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study. Not applicable.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability

of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Mary E Phillips <http://orcid.org/0000-0002-9033-9993>

John S Leeds <http://orcid.org/0000-0002-5140-6225>

Keith J Roberts <http://orcid.org/0000-0003-1799-9829>

REFERENCES

- Duggan SN, Smyth ND, O'Sullivan M, *et al*. The prevalence of malnutrition and fat-soluble vitamin deficiencies in chronic pancreatitis. *Nutr Clin Pract* 2014;29:348–54.
- DiMagno EP, Go VL, Summerskill WH. Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. *N Engl J Med* 1973;288:813–5.
- Bachmann J, Ketterer K, Marsch C, *et al*. Pancreatic cancer-related cachexia: influence on metabolism and correlation to weight loss and pulmonary function. *BMC Cancer* 2009;9:255.
- Armstrong T, Walters E, Varshney S, *et al*. Deficiencies of micronutrients, altered bowel function, and quality of life during late follow-up after pancreaticoduodenectomy for malignancy. *Pancreatology* 2002;2:528–34.
- Yamabe A, Irisawa A, Shibukawa G, *et al*. Early diagnosis of chronic pancreatitis: understanding the factors associated with the development of chronic pancreatitis. *Fukushima J Med Sci* 2017;63:1–7.
- de la Iglesia-Garcia D, Vallejo-Sendra N, Iglesias-Garcia J, *et al*. Increased risk of mortality associated with pancreatic exocrine insufficiency in patients with chronic pancreatitis. *J Clin Gastroenterol* 2018;52:e63–72.
- Partelli S, Frulloni L, Minniti C, *et al*. Faecal elastase-1 is an independent predictor of survival in advanced pancreatic cancer. *Dig Liver Dis* 2012;44:945–51.
- Roberts KJ, Bannister CA, Schrem H. Enzyme replacement improves survival among patients with pancreatic cancer: results of a population based study. *Pancreatology* 2019;19:114–21.
- Domínguez-Muñoz JE, Nieto-García L, López-Díaz J, *et al*. Impact of the treatment of pancreatic exocrine insufficiency on survival of patients with unresectable pancreatic cancer: a retrospective analysis. *BMC Cancer* 2018;18:534.
- D'Haese JG, Ceyhan GO, Demir IE, *et al*. Pancreatic enzyme replacement therapy in patients with exocrine pancreatic insufficiency due to chronic pancreatitis: a 1-year disease management study on symptom control and quality of life. *Pancreas* 2014;43:834–41.
- Sikkens ECM, Cahen DL, van Eijck C, *et al*. Patients with exocrine insufficiency due to chronic pancreatitis are undertreated: a Dutch national survey. *Pancreatology* 2012;12:71–3.
- Gooden HM, White KJ. Pancreatic cancer and supportive care—pancreatic exocrine insufficiency negatively impacts on quality of life. *Support Care Cancer* 2013;21:1835–41.



- 13 Guyatt GH, Oxman AD, Vist GE, *et al.* Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
- 14 Hoffmeister A, Mayerle J, Beglinger C, *et al.* English language version of the S3-consensus guidelines on chronic pancreatitis: Definition, aetiology, diagnostic examinations, medical, endoscopic and surgical management of chronic pancreatitis. *Z Gastroenterol* 2015;53:1447–95.
- 15 Toouli J, Biankin AV, Oliver MR, *et al.* Management of pancreatic exocrine insufficiency: Australasian pancreatic Club recommendations. *Med J Aust* 2010;193:461–7.
- 16 Keller J, Layer P. Human pancreatic exocrine response to nutrients in health and disease. *Gut* 2005;54 Suppl 6:1–28.
- 17 Chamokova B, Bastati N, Poetter-Lang S, *et al.* The clinical value of secretin-enhanced MRCP in the functional and morphological assessment of pancreatic diseases. *Br J Radiol* 2018;7:20170677.
- 18 Stevens T, Conwell DL, Zuccaro G, *et al.* A prospective crossover study comparing secretin-stimulated endoscopic and Dreiling tube pancreatic function testing in patients evaluated for chronic pancreatitis. *Gastrointest Endosc* 2008;67:458–66.
- 19 Hill PG. Faecal fat: time to give it up. *Ann Clin Biochem* 2001;38:164–7.
- 20 Dominici R, Franzini C. Fecal elastase-1 as a test for pancreatic function: a review. *Clin Chem Lab Med* 2002;40:325–32.
- 21 Stein J, Jung M, Sziegoleit A, *et al.* Immunoreactive elastase I: clinical evaluation of a new noninvasive test of pancreatic function. *Clin Chem* 1996;42:222–6.
- 22 Gredal C, Madsen LG, Larsen S. The Lundh test and faecal elastase 1 determination in chronic pancreatitis: a comparative study. *Pancreatology* 2003;3:389–94.
- 23 Lankisch PG, Schmidt I, König H, *et al.* Faecal elastase 1: not helpful in diagnosing chronic pancreatitis associated with mild to moderate exocrine pancreatic insufficiency. *Gut* 1998;42:551–4.
- 24 Leodolter A, Kahl S, Dominguez-Muñoz JE, *et al.* Comparison of two tubeless function tests in the assessment of mild-to-moderate exocrine pancreatic insufficiency. *Eur J Gastroenterol Hepatol* 2000;12:1335–8.
- 25 Loser C, Mollgaard A, Folsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. *Gut* 1996;39:580–6.
- 26 Lüth S, Teyssen S, Forssmann K, *et al.* Fecal elastase-1 determination: 'gold standard' of indirect pancreatic function tests? *Scand J Gastroenterol* 2001;36:1092–9.
- 27 Soldan W, Henker J, Sprössig C. Sensitivity and specificity of quantitative determination of pancreatic elastase 1 in feces of children. *J Pediatr Gastroenterol Nutr* 1997;24:53–5.
- 28 Walkowiak J, Cichy WK, Herzig KH. Comparison of fecal elastase-1 determination with the secretin-cholecystokinin test in patients with cystic fibrosis. *Scand J Gastroenterol* 1999;34:202–7.
- 29 Fischer B, Hoh S, Wehler M, *et al.* Faecal elastase-1: lyophilization of stool samples prevents false low results in diarrhoea. *Scand J Gastroenterol* 2001;36:771–4.
- 30 Tóth AZ, Szabó A, Hegyi E, *et al.* Detection of human elastase isoforms by the ScheBo pancreatic elastase 1 test. *Am J Physiol Gastrointest Liver Physiol* 2017;312:G606–14.
- 31 Borowitz D, Lin R, Baker SS. Comparison of monoclonal and polyclonal ELISAs for fecal elastase in patients with cystic fibrosis and pancreatic insufficiency. *J Pediatr Gastroenterol Nutr* 2007;44:219–23.
- 32 Loh KW, Vriens MR, Gerritsen A, *et al.* Unintentional weight loss is the most important indicator of malnutrition among surgical cancer patients. *Neth J Med* 2012;70:365–9.
- 33 Schnelldorfer T, Adams DB. The effect of malnutrition on morbidity after surgery for chronic pancreatitis. *Am Surg* 2005;71:466–73.
- 34 Kondrup J, Rasmussen HH, Hamberg O. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clinical Nutrition* 2003;22:321–36.
- 35 Sorensen J, Kondrup J, Prokopowicz J, *et al.* EuroOOPS: an international, multicentre study to implement nutritional risk screening and evaluate clinical outcome. *Clinical Nutrition* 2008;27:340–9.
- 36 Sikkens ECM, Cahen DL, de Wit J, *et al.* Prospective assessment of the influence of pancreatic cancer resection on exocrine pancreatic function. *British Journal of Surgery* 2013;101:109–13.
- 37 Dumasy V, Delhaye M, Cotton F, *et al.* Fat malabsorption screening in chronic pancreatitis. *Am J Gastroenterol* 2004;99:1350–4.
- 38 Rasmussen HH, Irtun O, Olesen SS. Nutrition in chronic pancreatitis. *World J Gastroenterol* 2013;19:7267–75.
- 39 Tinju J, Reshmi S, Rajesh G, *et al.* Anthropometric, biochemical, clinical and dietary assessment for malnutrition in South Indian patients with chronic pancreatitis. *Trop Gastroenterol* 2010;31:285–90.
- 40 Kalvaria I, Labadarios D, Shephard GS, *et al.* Biochemical vitamin E deficiency in chronic pancreatitis. *Int J Pancreatol* 1986;1:119–28.
- 41 Marotta F, Labadarios D, Frazer L, *et al.* Fat-Soluble vitamin concentration in chronic alcohol-induced pancreatitis. Relationship with steatorrhea. *Dig Dis Sci* 1994;39:993–8.
- 42 Nakamura T, Takebe K, Imamura K, *et al.* Fat-Soluble vitamins in patients with chronic pancreatitis (pancreatic insufficiency). *Acta Gastroenterol Belg* 1996;59:10–14.
- 43 Lindkvist B, Dominguez-Muñoz JE, Luaces-Regueira M, *et al.* Serum nutritional markers for prediction of pancreatic exocrine insufficiency in chronic pancreatitis. *Pancreatology* 2012;12:305–10.
- 44 Livingstone C, Davis J, Marvin V, *et al.* Vitamin A deficiency presenting as night blindness during pregnancy. *Ann Clin Biochem* 2003;40:292–4.
- 45 Sikkens ECM, Cahen DL, Koch AD, *et al.* The prevalence of fat-soluble vitamin deficiencies and a decreased bone mass in patients with chronic pancreatitis. *Pancreatology* 2013;13:238–42.
- 46 Martínez-Moneo E, Stigliano S, Hedström A, *et al.* Deficiency of fat-soluble vitamins in chronic pancreatitis: a systematic review and meta-analysis. *Pancreatology* 2016;16:988–94.
- 47 Vujasinovic M, Hedström A, Maisonneuve P, *et al.* Zinc deficiency in patients with chronic pancreatitis. *World J Gastroenterol* 2019;25:600–7.
- 48 Dutta SK, Bustin MP, Russell RM. Deficiency of fat-soluble vitamins in treated patients with pancreatic insufficiency. *Ann Intern Med* 1982;97:549–52.
- 49 Conwell DL, Lee LS, Yadav D, *et al.* American pancreatic association practice guidelines in chronic pancreatitis: evidence-based report on diagnostic guidelines. *Pancreas* 2014;43:1143–62.
- 50 Luetmer PH, Stephens DH, Ward EM. Chronic pancreatitis: reassessment with current CT. *Radiology* 1989;171:353–7.
- 51 Kim DH, Pickhardt PJ. Radiologic assessment of acute and chronic pancreatitis. *Surg Clin North Am* 2007;87:1341–58.
- 52 Dominguez-Muñoz JE, Manes G, Pieramico O, *et al.* Effect of pancreatic ductal and parenchymal changes on exocrine function in chronic pancreatitis. *Pancreas* 1995;10:31–5.
- 53 Yamada Y, Mori H, Matsumoto S, *et al.* Pancreatic adenocarcinoma versus chronic pancreatitis: differentiation with triple-phase helical CT. *Abdom Imaging* 2010;35:163–71.
- 54 Scuro LA, Cavallini G, Benini L, *et al.* Pancreatic calcifications in patients with chronic pancreatitis. A sign of long-lasting or severe disease? *Int J Pancreatol* 1990;6:139–50.
- 55 Lankisch PG, Otto J, Erkelenz I, *et al.* Pancreatic calcifications: no indicator of severe exocrine pancreatic insufficiency. *Gastroenterology* 1986;90:617–21.
- 56 Malfertheiner P, Büchler M. Correlation of imaging and function in chronic pancreatitis. *Radiol Clin North Am* 1989;27:51–64.
- 57 Malfertheiner P, Büchler M, Stanescu A, *et al.* Exocrine pancreatic function in correlation to ductal and parenchymal morphology in chronic pancreatitis. *Hepatology* 1986;33:110–4.
- 58 Anaizi A, Hart PA, Conwell DL. Diagnosing chronic pancreatitis. *Dig Dis Sci* 2017;62:1713–20.
- 59 Bilgin M, Bilgin S, Balci NC, *et al.* Magnetic resonance imaging and magnetic resonance cholangiopancreatography findings compared with fecal elastase 1 measurement for the diagnosis of chronic pancreatitis. *Pancreas* 2008;36:e33–9.
- 60 Balci NC, Smith A, Momtahan AJ, *et al.* MRI and S-MRCP findings in patients with suspected chronic pancreatitis: correlation with endoscopic pancreatic function testing (ePFT). *J Magn Reson Imaging* 2010;31:601–6.
- 61 Albashir S, Bronner MP, Parsi MA, *et al.* Endoscopic ultrasound, secretin endoscopic pancreatic function test, and histology: correlation in chronic pancreatitis. *Am J Gastroenterol* 2010;105:2498–503.
- 62 Chong AKH, Hawes RH, Hoffman BJ, *et al.* Diagnostic performance of EUS for chronic pancreatitis: a comparison with histopathology. *Gastrointest Endosc* 2007;65:808–14.
- 63 Trikudanathan G, Munigala S, Barlass U, *et al.* Evaluation of Rosemont criteria for non-calcific chronic pancreatitis (NCCP) based on histopathology - A retrospective study. *Pancreatology* 2017;17:63–9.
- 64 Dominguez-Muñoz JE, Álvarez-Castro A, Lariño-Noia J, *et al.* Endoscopic ultrasonography of the pancreas as an indirect method to predict pancreatic exocrine insufficiency in patients with chronic pancreatitis. *Pancreas* 2012;41:724–8.
- 65 Dominguez-Muñoz JE, Iglesias-García J, Castiñeira Alvariño M, *et al.* EUS elastography to predict pancreatic exocrine insufficiency

- in patients with chronic pancreatitis. *Gastrointest Endosc* 2015;81:136–42.
- 66 Chowdhury R, Bhutani MS, Mishra G, *et al.* Comparative analysis of direct pancreatic function testing versus morphological assessment by endoscopic ultrasonography for the evaluation of chronic unexplained abdominal pain of presumed pancreatic origin. *Pancreas* 2005;31:63–8.
 - 67 Duggan SN, Ni Chonchubhair HM, Lawal O, *et al.* Chronic pancreatitis: a diagnostic dilemma. *World J Gastroenterol* 2016;22:2304–13.
 - 68 Capurso G, Traini M, Piciocchi M, *et al.* Exocrine pancreatic insufficiency: prevalence, diagnosis, and management. *Clin Exp Gastroenterol* 2019;12:129–39.
 - 69 Xu Y, Wu D, Zeng Y, *et al.* Pancreatic exocrine function and morphology following an episode of acute pancreatitis. *Pancreas* 2012;41:922–7.
 - 70 Huang W, de la Iglesia-García D, Baston-Rey I, *et al.* Exocrine pancreatic insufficiency following acute pancreatitis: systematic review and meta-analysis. *Dig Dis Sci* 2019;64:1985–2005.
 - 71 Hollemans RA, Bakker OJ, Boermeester MA, *et al.* Superiority of step-up approach vs open necrosectomy in long-term follow-up of patients with necrotizing pancreatitis. *Gastroenterology* 2019;156:1016–26.
 - 72 Wigmore SJ, Plester CE, Richardson RA, *et al.* Changes in nutritional status associated with unresectable pancreatic cancer. *Br J Cancer* 1997;75:106–9.
 - 73 Saito T, Hirano K, Isayama H, *et al.* The role of pancreatic enzyme replacement therapy in unresectable pancreatic cancer. *Pancreas* 2017;46:341–6.
 - 74 Sikkens ECM, Cahen DL, de Wit J, *et al.* A prospective assessment of the natural course of the exocrine pancreatic function in patients with a pancreatic head tumor. *J Clin Gastroenterol* 2014;48:e43–6.
 - 75 National Institute for Health and Care Excellence (NICE). Pancreatic cancer in adults: diagnosis and management. NICE guideline [NG85], 2018. Available: <https://www.nice.org.uk/guidance/ng85> [Accessed 8 Mar 2021].
 - 76 Woo SM, Joo J, Kim SY, *et al.* Efficacy of pancreatic exocrine replacement therapy for patients with unresectable pancreatic cancer in a randomized trial. *Pancreatol* 2016;16:1099–105.
 - 77 Bruno MJ, Haverkort EB, Tijssen GP, *et al.* Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region. *Gut* 1998;42:92–6.
 - 78 Saito T, Nakai Y, Isayama H, *et al.* A multicenter open-label randomized controlled trial of pancreatic enzyme replacement therapy in unresectable pancreatic cancer. *Pancreas* 2018;47:800–6.
 - 79 Jang J-Y, Kim S-W, Park S-J, *et al.* Comparison of the functional outcome after pylorus-preserving pancreatoduodenectomy: pancreatogastrostomy and pancreatojejunostomy. *World J Surg* 2002;26:366–71.
 - 80 Roeyen G, Jansen M, Hartman V, *et al.* The impact of pancreatoduodenectomy on endocrine and exocrine pancreatic function: a prospective cohort study based on pre- and postoperative function tests. *Pancreatol* 2017;17:974–82.
 - 81 Tseng DSJ, Molenaar IQ, Besselink MG, *et al.* Pancreatic exocrine insufficiency in patients with pancreatic or periampullary cancer. *Pancreas* 2016;45:325–30.
 - 82 Singh VK, Haupt ME, Geller DE, *et al.* Less common etiologies of exocrine pancreatic insufficiency. *World J Gastroenterol* 2017;23:7059–76.
 - 83 Ewald N, Raspe A, Kaufmann C, *et al.* Determinants of exocrine pancreatic function as measured by fecal elastase-1 concentrations (FEC) in patients with diabetes mellitus. *Eur J Med Res* 2009;14:118–22.
 - 84 Hardt PD, Hauenschild A, Nalop J, *et al.* High prevalence of exocrine pancreatic insufficiency in diabetes mellitus. A multicenter study screening fecal elastase 1 concentrations in 1,021 diabetic patients. *Pancreatol* 2003;3:395–402.
 - 85 Ewald N, Bretzel RG, Fantus IG, *et al.* Pancreatin therapy in patients with insulin-treated diabetes mellitus and exocrine pancreatic insufficiency according to low fecal elastase 1 concentrations. Results of a prospective multi-centre trial. *Diabetes Metab Res Rev* 2007;23:386–91.
 - 86 Pannala R, Basu A, Petersen GM, *et al.* New-Onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. *Lancet Oncol* 2009;10:88–95.
 - 87 Rothenbacher D, Löw M, Hardt PD, *et al.* Prevalence and determinants of exocrine pancreatic insufficiency among older adults: results of a population-based study. *Scand J Gastroenterol* 2005;40:697–704.
 - 88 Campbell JA, Sanders DS, Francis KA, *et al.* Should we investigate gastroenterology patients for pancreatic exocrine insufficiency? a dual centre UK study. *J Gastrointest Liver Dis* 2016;25:303–9.
 - 89 Czako L, Takács T, Hegyi P, *et al.* Quality of life assessment after pancreatic enzyme replacement therapy in chronic pancreatitis. *Can J Gastroenterol* 2003;17:597–603.
 - 90 Kahl S, Schütte K, Glasbrenner B, *et al.* The effect of oral pancreatic enzyme supplementation on the course and outcome of acute pancreatitis: a randomized, double-blind parallel-group study. *JOP* 2014;15:165–74.
 - 91 Ramesh H, Reddy N, Bhatia S, *et al.* A 51-week, open-label clinical trial in India to assess the efficacy and safety of pancreatin 40000 enteric-coated minimicrospheres in patients with pancreatic exocrine insufficiency due to chronic pancreatitis. *Pancreatol* 2013;13:133–9.
 - 92 Winny M, Paroglou V, Bektas H, *et al.* Insulin dependence and pancreatic enzyme replacement therapy are independent prognostic factors for long-term survival after operation for chronic pancreatitis. *Surgery* 2014;155:271–9.
 - 93 Barkin JA, Westermann A, Hoos W, *et al.* Frequency of appropriate use of pancreatic enzyme replacement therapy and symptomatic response in pancreatic cancer patients. *Pancreas* 2019;48:780–6.
 - 94 Dunleavy L, Al-Mukhtar A, Halliday V. Pancreatic enzyme replacement therapy following surgery for pancreatic cancer: an exploration of patient self-management. *Clinical Nutrition ESPEN* 2018;26:97–103.
 - 95 Johnson CD, Williamson N, Janssen-van Solingen G, *et al.* Psychometric evaluation of a patient-reported outcome measure in pancreatic exocrine insufficiency (PEI). *Pancreatol* 2019;19:182–90.
 - 96 Konstan MW, Wagener JS, Wilschanski M, *et al.* A comparison of liprotamase, a non-porcine pancreatic enzyme replacement therapy, to porcine extracted pancrelipase in a noninferiority randomized clinical trial in patients with cystic fibrosis. *Clin Investig* 2018;08:147–54.
 - 97 Pancreatic Cancer Action. Pancreatic cancer: nutrition, 2021. Available: <https://pancreaticcanceraction.org/healthcare-professionals/patients-journey/nutrition-for-your-patient/> [Accessed 8 Mar 2021].
 - 98 Seiler CM, Izbicki J, Varga-Szabó L, *et al.* Randomised clinical trial: a 1-week, double-blind, placebo-controlled study of pancreatin 25 000 Ph. Eur. minimicrospheres (Creon 25000 MMS) for pancreatic exocrine insufficiency after pancreatic surgery, with a 1-year open-label extension. *Aliment Pharmacol Ther* 2013;37:691–702.
 - 99 Halm U, Löser C, Löhr M, *et al.* A double-blind, randomized, multicentre, crossover study to prove equivalence of pancreatin minimicrospheres versus microspheres in exocrine pancreatic insufficiency. *Aliment Pharmacol Ther* 1999;13:951–7.
 - 100 Neoptolemos JP, Ghaneh P, Andrén-Sandberg A, *et al.* Treatment of pancreatic exocrine insufficiency after pancreatic resection. Results of a randomized, double-blind, placebo-controlled, crossover study of high vs standard dose pancreatin. *Int J Pancreatol* 1999;25:171–80.
 - 101 Dominguez-Munoz JE, Iglesias-Garcia J, Iglesias-Rey M, *et al.* Effect of the administration schedule on the therapeutic efficacy of oral pancreatic enzyme supplements in patients with exocrine pancreatic insufficiency: a randomized, three-way crossover study. *Aliment Pharmacol Ther* 2005;21:993–1000.
 - 102 Castiñeira-Alvarino M, Lindkvist B, Luaces-Regueira M, *et al.* The role of high fat diet in the development of complications of chronic pancreatitis. *Clinical Nutrition* 2013;32:830–6.
 - 103 Singh S, Midha S, Singh N, *et al.* Dietary counseling versus dietary supplements for malnutrition in chronic pancreatitis: a randomized controlled trial. *Clin Gastroenterol Hepatol* 2008;6:353–9.
 - 104 Dutta SK, Hlasko J. Dietary fiber in pancreatic disease: effect of high fiber diet on fat malabsorption in pancreatic insufficiency and in vitro study of the interaction of dietary fiber with pancreatic enzymes. *Am J Clin Nutr* 1985;41:517–25.
 - 105 Tiengou L-E, Gloor R, Pouzoulet J, *et al.* Semi-elemental formula or polymeric formula: is there a better choice for enteral nutrition in acute pancreatitis? randomized comparative study. *JPEN J Parenter Enteral Nutr* 2006;30:1–5.
 - 106 Meier R, Ockenga J, Pertkiewicz M, *et al.* ESPEN guidelines on enteral nutrition: pancreas. *Clin Nutr* 2006;25:275–84.
 - 107 Arvanitakis M, Ockenga J, Bezmarevic M, *et al.* ESPEN guideline on clinical nutrition in acute and chronic pancreatitis. *Clin Nutr* 2020;39:612–31.
 - 108 Vecht J, Symersky T, Lamers CBHW, *et al.* Efficacy of lower than standard doses of pancreatic enzyme supplementation therapy during acid inhibition in patients with pancreatic exocrine insufficiency. *J Clin Gastroenterol* 2006;40:721–5.



- 109 Heijerman HGM, Lamers CBHW, Bakker W, *et al.* Improvement of fecal fat excretion after addition of omeprazole to pancrease in cystic fibrosis is related to residual exocrine function of the pancreas. *Dig Dis Sci* 1993;38:1–6.
- 110 Nakamura T, Takebe K, Kudoh K, *et al.* Effects of pancreatic digestive enzymes, sodium bicarbonate, and a proton pump inhibitor on steatorrhea caused by pancreatic diseases. *J Int Med Res* 1995;23:37–47.
- 111 Sander-Struckmeier S, Beckmann K, Janssen-van Solingen G, *et al.* Retrospective analysis to investigate the effect of concomitant use of gastric Acid-Suppressing drugs on the efficacy and safety of Pancrelipase/Pancreatin (CREON®) in patients with pancreatic exocrine insufficiency. *Pancreas* 2013;42:983–9.
- 112 Bruno MJ, Rauws EAJ, Hoek FJ, *et al.* Comparative effects of adjuvant cimetidine and omeprazole during pancreatic enzyme replacement therapy. *Dig Dis Sci* 1994;39:988–92.
- 113 Jang J-Y, Kim S-W, Han J-K, *et al.* Randomized prospective trial of the effect of induced hypergastrinemia on the prevention of pancreatic atrophy after pancreatoduodenectomy in humans. *Ann Surg* 2003;237:522–9.
- 114 Lanás-Gimeno A, Hijos G, Lanás Ángel. Proton pump inhibitors, adverse events and increased risk of mortality. *Expert Opin Drug Saf* 2019;18:1043–53.
- 115 Richter JE, Kahrlas PJ, Johanson J, *et al.* Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. *Am J Gastroenterol* 2001;96:656–65.
- 116 Mylan Products Limited. *Creon micro pancreatin 60.12 Mg Gastro-resistant granules, Creon 10000 capsules, Creon 25000 capsules: prescribing information*, 2018.
- 117 Janssen-Cilag Limited. *Pancrease HL capsules summary of product characteristics*, 2020.
- 118 Merck Serono Limited. *Nutrizym 22 summary of product characteristics*, 2018.
- 119 Essential Pharmaceuticals Limited. *Pancrex V capsules summary of product characteristics*, 2017.
- 120 Atkinson SN. A comparative study of the enzyme activity, acid resistance and dissolution characteristics of four enteric coated microsphere preparations of pancreatin. *Eur J Clin Res* 1991;1:37–45.
- 121 Littlewood JM, Kelleher J, Walters MP, *et al.* In vivo and in vitro studies of microsphere pancreatic supplements. *J Pediatr Gastroenterol Nutr* 1988;7:S22–9.
- 122 Gan KH, Geus WP, Bakker W, *et al.* In vitro dissolution profiles of enteric-coated microsphere/microtablet pancreatin preparations at different pH values. *Aliment Pharmacol Ther* 1996;10:771–5.
- 123 Shlieout G, Koerner A, Maffert M, *et al.* Administration of CREON® Pancrelipase pellets via gastrostomy tube is feasible with no loss of gastric resistance or lipase activity. *Clin Drug Investig* 2011;31:e1–7.
- 124 Ferrie S, Graham C, Hoyle M. Pancreatic enzyme supplementation for patients receiving enteral feeds. *Nutr Clin Pract* 2011;26:349–51.
- 125 Phillips ME, Berry A, Gettle LS. Pancreatic exocrine insufficiency and enteral feeding: a practical guide with case studies. *Pract Gastroenterol* 2018;XLII:181.
- 126 Silk DBA. Formulation of enteral diets for use in jejunal enteral feeding. *Proc Nutr Soc* 2008;67:270–2.
- 127 Capurso G, Signoretti M, Archibugi L, *et al.* Systematic review and meta-analysis: small intestinal bacterial overgrowth in chronic pancreatitis. *United European Gastroenterol J* 2016;4:697–705.
- 128 O'Reilly DA, McPherson SJ, Sinclair MT, *et al.* 'Treat the Cause': the NCEPOD report on acute pancreatitis. *Br J Hosp Med* 2017;78:6–7.
- 129 Ruiz-Campos L, Gisbert JP, Ysamat M, *et al.* Systematic review with meta-analysis: the prevalence of bile acid malabsorption and response to colestyramine in patients with chronic watery diarrhoea and previous cholecystectomy. *Aliment Pharmacol Ther* 2019;49:242–50.
- 130 Sciarretta G, Furno A, Mazzoni M, *et al.* Post-Cholecystectomy diarrhea: evidence of bile acid malabsorption assessed by SeHCAT test. *Am J Gastroenterol* 1992;87:1852–4.
- 131 Leeds JS, Hopper AD, Sidhu R, *et al.* Some patients with irritable bowel syndrome may have exocrine pancreatic insufficiency. *Clin Gastroenterol Hepatol* 2010;8:433–8.
- 132 Talley NJ, Holtmann G, Nguyen QN, *et al.* Undiagnosed pancreatic exocrine insufficiency and chronic pancreatitis in functional GI disorder patients with diarrhea or abdominal pain. *J Gastroenterol Hepatol* 2017;32:1813–7.
- 133 Arasaradnam RP, Brown S, Forbes A, *et al.* Guidelines for the investigation of chronic diarrhoea in adults: British Society of gastroenterology, 3rd edition. *Gut* 2018;67:1380–99.
- 134 Phillips M, Lordan JT, Menezes N, *et al.* Feeding patients following pancreaticoduodenectomy: a UK national survey. *Annals* 2009;91:385–8.
- 135 Pezzilli R, Morselli Labate AM, Fantini L, *et al.* Quality of life and clinical indicators for chronic pancreatitis patients in a 2-year follow-up study. *Pancreas* 2007;34:191–6.
- 136 Pendharkar SA, Salt K, Plank LD, *et al.* Quality of life after acute pancreatitis: a systematic review and meta-analysis. *Pancreas* 2014;43:1194–200.
- 137 National Institute for Health and Care Excellence (NICE). Pancreatitis. NICE guideline [NG104], 2018. Available: <https://www.nice.org.uk/guidance/ng104> [Accessed 8 Mar 2021].
- 138 Phillips ME. Pancreatic exocrine insufficiency following pancreatic resection. *Pancreatol* 2015;15:449–55.
- 139 Min M, Patel B, Han S, *et al.* Exocrine pancreatic insufficiency and malnutrition in chronic pancreatitis: identification, treatment, and consequences. *Pancreas* 2018;47:1015–8.
- 140 Haas S, Krins S, Knauerhase A, *et al.* Altered bone metabolism and bone density in patients with chronic pancreatitis and pancreatic exocrine insufficiency. *JOP* 2015;16:58–62.
- 141 Mann STW, Mann V, Stracke H, *et al.* Fecal elastase 1 and vitamin D3 in patients with osteoporotic bone fractures. *Eur J Med Res* 2008;13:68–72.
- 142 Morán CE, Sosa EG, Martínez SM, *et al.* Bone mineral density in patients with pancreatic insufficiency and steatorrhea. *Am J Gastroenterol* 1997;92:867–71.
- 143 Duggan SN, Smyth ND, Murphy A, *et al.* High prevalence of osteoporosis in patients with chronic pancreatitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2014;12:219–28.
- 144 Drozdov VN, Chernyshova IV VLV, *et al.* [Role of exocrine pancreatic insufficiency in reducing of the bone mineral density in patients with chronic pancreatitis]. *Eksp Klin Gastroenterol* 2010;8:17–22.
- 145 Gubergrits N, Kutyrykina IL. Mineral density of bones in chronic pancreatitis. *Pancreatol* 2011;11:S1–80.
- 146 Mann STW, Stracke H, Lange U, *et al.* Alterations of bone mineral density and bone metabolism in patients with various grades of chronic pancreatitis. *Metabolism* 2003;52:579–85.
- 147 Sikkens ECM, Cahen DL, Kuipers EJ, *et al.* Su1254 prospective evaluation of the prevalence of fat-soluble vitamin deficiencies and decreased bone mineral density in chronic pancreatitis. *Gastroenterology* 2012;142:Abstract Su1254:S461–S-462.
- 148 Sudeep K, Chacko A, Thomas N, *et al.* Predictors of osteodystrophy in patients with chronic nonalcoholic pancreatitis with or without diabetes. *Endocr Pract* 2011;17:897–905.
- 149 Duggan SN, O'Sullivan M, Hamilton S, *et al.* Patients with chronic pancreatitis are at increased risk for osteoporosis. *Pancreas* 2012;41:1119–24.
- 150 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;5:153–99.
- 151 Thorat V, Reddy N, Bhatia S, *et al.* Randomised clinical trial: the efficacy and safety of pancreatin enteric-coated minimicrospheres (Creon 40000 MMS) in patients with pancreatic exocrine insufficiency due to chronic pancreatitis—a double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2012;36:426–36.
- 152 Whitcomb DC, Lehman GA, Vasileva G, *et al.* Pancrelipase delayed-release capsules (CREON) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: a double-blind randomized trial. *Am J Gastroenterol* 2010;105:2276–86.
- 153 Gubergrits N, Malecka-Panas E, Lehman GA, *et al.* A 6-month, open-label clinical trial of pancrelipase delayed-release capsules (Creon) in patients with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery. *Aliment Pharmacol Ther* 2011;33:1152–61.
- 154 Whitcomb DC, Bodhani A, Beckmann K, *et al.* Efficacy and safety of pancrelipase/pancreatin in patients with exocrine pancreatic insufficiency and a medical history of diabetes mellitus. *Pancreas* 2016;45:679–86.
- 155 Häusler M, Meilicke R, Biesterfeld S, *et al.* First adult patient with fibrosing COLONOPATHY. *Am J Gastroenterol* 1998;93:1171–2.
- 156 Ramsden WH, Moya EF, Littlewood JM. Colonic wall thickness, pancreatic enzyme dose and type of preparation in cystic fibrosis. *Arch Dis Child* 1998;79:339–43.
- 157 Dodge JA. Pancreatic enzymes and fibrosing Colonopathy. *J Cyst Fibros* 2015;14:153.
- 158 Hardt PD, Krauss A, Bretz L, *et al.* Pancreatic exocrine function in patients with type 1 and type 2 diabetes mellitus. *Acta Diabetol* 2000;37:105–10.

- 159 Dietary reference values for food energy and nutrients for the United Kingdom. Report of the panel on dietary reference values of the Committee on medical aspects of food policy. *Rep Health Soc Subj* 1991;41:1-210.
- 160 Taylor CJ. Fibrosing colonopathy unrelated to pancreatic enzyme supplementation. *J Pediatr Gastroenterol Nutr* 2002;35:268-9.
- 161 Serban DE, Florescu P, Miu N. Fibrosing colonopathy revealing cystic fibrosis in a neonate before any pancreatic enzyme supplementation. *J Pediatr Gastroenterol Nutr* 2002;35:356-9.
- 162 Icks A, Haastert B, Giani G, et al. Low fecal elastase-1 in type I diabetes mellitus. *Z Gastroenterol* 2001;39:823-30.
- 163 Mancilla A C, Hurtado H C, Tobar A E, et al. [Pancreatic exocrine function in diabetes mellitus. Determination of fecal elastase]. *Rev Med Chil* 2006;134:407-14.
- 164 Nunes ACR, Pontes JM, Rosa A, et al. Screening for pancreatic exocrine insufficiency in patients with diabetes mellitus. *Am J Gastroenterol* 2003;98:2672-5.
- 165 Gullo L, Simoni P, Migliori M, et al. A study of pancreatic function among subjects over ninety years of age. *Pancreatology* 2009;9:240-4.
- 166 Herzig K-H, Purhonen A-K, Räsänen KM, et al. Fecal pancreatic elastase-1 levels in older individuals without known gastrointestinal diseases or diabetes mellitus. *BMC Geriatr* 2011;11:4.
- 167 Griesche-Philippi J, Otto J, Schwörer H, et al. Exocrine pancreatic function in patients with end-stage renal disease. *Clin Nephrol* 2010;74:457-64.
- 168 Ventrucci M, Cipolla A, Middonno M, et al. Impaired fecal elastase excretion in uremic pancreopathy. *Dig Dis Sci* 2000;45:2265-9.
- 169 Kauppi M, Kankaanpää E, Kautiainen H. Exocrine dysfunction of the pancreas in patients with chronic polyarthritis. *J Clin Rheumatol* 2001;7:166-9.
- 170 Abdulkarim AS, Burgart LJ, See J, et al. Etiology of nonresponsive celiac disease: results of a systematic approach. *Am J Gastroenterol* 2002;97:2016-21.
- 171 Evans KE, Leeds JS, Morley S, et al. Pancreatic insufficiency in adult celiac disease: do patients require long-term enzyme supplementation? *Dig Dis Sci* 2010;55:2999-3004.
- 172 Leeds JS, Hopper AD, Hurlstone DP, et al. Is exocrine pancreatic insufficiency in adult coeliac disease a cause of persisting symptoms? *Aliment Pharmacol Ther* 2007;25:265-71.
- 173 Barthet M, Lesavre N, Desplats S, et al. Frequency and characteristics of pancreatitis in patients with inflammatory bowel disease. *Pancreatology* 2006;6:464-71.
- 174 Maconi G, Dominici R, Molteni M, et al. Prevalence of pancreatic insufficiency in inflammatory bowel diseases. assessment by fecal elastase-1. *Dig Dis Sci* 2008;53:262-70.
- 175 Carroccio A, Di Prima L, Di Grigoli C, et al. Exocrine pancreatic function and fat malabsorption in human immunodeficiency virus-infected patients. *Scand J Gastroenterol* 1999;34:729-34.
- 176 Carroccio A, Fontana M, Spagnuolo MI, et al. Pancreatic dysfunction and its association with fat malabsorption in HIV infected children. *Gut* 1998;43:558-63.
- 177 Angelini G, Merigo F, Degani G, et al. Association of chronic alcoholic liver and pancreatic disease: a prospective study. *Am J Gastroenterol* 1985;80:998-1003.
- 178 Aparisi L, Sabater L, Del-Olmo J, et al. Does an association exist between chronic pancreatitis and liver cirrhosis in alcoholic subjects? *World J Gastroenterol* 2008;14:6171-9.
- 179 Caradonna P, Costamagna G, Benedetti G, et al. Chronic pancreatitis prevalence in liver cirrhosis. morphological and functional study. *Ital J Gastroenterol* 1996;28:91-4.
- 180 Hayakawa T, Kondo T, Shibata T, et al. Exocrine pancreatic function in chronic liver diseases. *Am J Gastroenterol* 1991;86:201-4.
- 181 Lamarca A, McCallum L, Nuttall C, et al. Somatostatin analogue-induced pancreatic exocrine insufficiency in patients with neuroendocrine tumors: results of a prospective observational study. *Expert Rev Gastroenterol Hepatol* 2018;12:723-31.
- 182 Powell CJ. Colonic toxicity from pancreatins: a contemporary safety issue. *Lancet* 1999;353:911-5.

A consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines

Supplemental material

Authors: Mary Phillips,¹ Andrew Hopper,² John Leeds,³ Keith J Roberts,⁴ Laura McGeeney,⁵ Sinead N Duggan,⁶ and Rajesh Kumar¹

Affiliations: ¹Royal Surrey Hospital NHS Foundation Trust, Guildford, UK; ²Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK; ³Newcastle Upon Tyne Teaching Hospitals NHS Foundation Trust, Newcastle Upon Tyne, UK; ⁴Nuffield House, Queen Elizabeth Hospital Birmingham, Edgbaston, Birmingham, UK; ⁵Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; ⁶Trinity College Dublin, Dublin, Ireland

METHODOLOGY

Literature search details

Systematic literature search details are outlined in **table S1**. The initial literature searches were performed between October and December 2018. Prior to submission, literature searches were updated to include additional articles published up to and including 22 May 2020.

Table S1. Literature search strategy (PubMed)

Search	Literature search terms ^{a-c}
1	Diagnosis, definition, faecal elastase, fecal elastase, steatorrhoea, nutritional deficiencies, micronutrient, magnesium, trace elements, fat soluble vitamins, faecal fat, fecal fat, coefficient of fat absorption, endoscopic ultrasound, secretin, MRCP, Magnetic resonance cholangiopancreatography, s-MRCP, CT, Computerised tomography, triglyceride breath test, duodenal juice collection
2	Survival, quality of life, pancreatic cancer, pancreatic adenocarcinoma, pancreatic ductal adenocarcinoma, periampullary cancer, pancreatoduodenectomy, pancreaticoduodenectomy, whipples, distal pancreatectomy, progression, natural history, natural course
3	Bone density, absorptiometry, photon, bone diseases, metabolic, osteoporosis, osteopenia, osteomalacia, osteopathy
4	Acute pancreatitis, severe pancreatitis, necrotising pancreatitis
5	SIBO, SBBO, small intestinal bacterial overgrowth, small bowel bacterial overgrown, BAM, bile acid malabsorption, coeliac, celiac, TTG, tissue, transglutaminase, PPI, proton pump inhibitor, laxatives, chemotherapy, lactase deficiency, lactose intolerance, colorectal cancer, pancreatic cancer, IBD, inflammatory bowel disease, irritable bowel syndrome, IBS
6	Management, treatment, guidance, dose, timing, time, frequency, administration, capsule, microspheres, minitabs, increase, efficacy, side effects
7	Long term, follow up, monitoring, review
8	Quality of life, performance status, PROMS, patient reported outcome measures, outcome measures
g ^{d,e}	Pancreatin AND (pregnancy, breastfeeding, gout, fibrosing colonopathy, safety) AND Pancreatic exocrine insufficiency AND therapy AND safety

^aSearches 1–8 used core search criteria (PERT OR Pancreatin OR Pancreatic Exocrine Insufficiency OR Exocrine Pancreatic Insufficiency OR Pancreas Insufficiency OR Pancreatic Insufficiency AND ≥1980) with specific literature search terms for each section as indicated; ^bsearch filters: terms appear in the abstract/title; human participants; English-language; randomised controlled trials, meta-analyses and observational studies; ^cscreening: adults >18 years of age were included; ^dcore search terms or filters were not used; ^epublication date: >1998

BAM, bile acid malabsorption; CT, computed tomography; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; PERT, pancreatic enzyme replacement therapy; PPI, proton-pump inhibitor; PROMS, patient-reported outcome measures; QoL, quality of life; SIBO, small intestinal bacterial overgrowth; SBBO, small bowel bacterial overgrowth; sMRCP, secretin injection at magnetic resonance cholangiopancreatography; TTG, tissue transglutaminase

Bone health literature searches

Only one paper was retrieved on the effect of pancreatic exocrine insufficiency (PEI) on bone health. However, this meta-analysis of nine studies did not examine the association between PEI and vitamin D deficiency or bone health and was, therefore, excluded. Prior to applying the search filters (specifically: terms appear in abstract/title, human, English language, abstract, meta-analysis/observational study/randomised controlled trial), 63 papers were retrieved, and these were reviewed to ensure that they had not been incorrectly excluded. Of the 63 papers, four were potentially relevant. The remaining papers were further excluded (reviews: n=20; not relevant: n=24; studies on children: n=7; non-English language: n=7). The search was repeated to ensure that papers had not been inappropriately excluded.

LESS COMMON CAUSES OF PEI: STATEMENTS AND SUPPORTING EVIDENCE

Statement 2.5.1: Ageing populations may have an increased prevalence of PEI and, therefore, should be considered for testing, particularly if presenting with unexplained weight loss or diarrhoea (good practice point [GPP]; 88% agreement)

Comments

Several studies have investigated the prevalence of PEI in the elderly using the FEL-1 diagnostic test. One study in individuals aged 50–75 years of age found that 105/914 (11.5%) had a FEL-1 level $<200 \mu\text{g/g}$ stool.¹ Other studies have shown that PEI increases with increasing age.^{2,3}

Statement 2.5.2: Patients with renal disease and rheumatological conditions may have an increased prevalence of PEI, but further studies are needed before routine testing can be recommended (GPP; 95% agreement)

Comments

Several other conditions have been associated with PEI, but high-quality studies examining prevalence, or the value of PERT are lacking. Sjögren's syndrome has been associated with PEI, although a recent study only showed a prevalence of 4%.⁴ Similarly, patients with advanced renal disease are commonly malnourished and PEI has been implicated in the pathogenesis. Two small studies measured FEL-1 levels (using different cut-offs) in patients undergoing dialysis and found FEL-1 levels $<100 \mu\text{g/g}$ stool in 12/25 (48%) and FEL-1 levels of 1–200 $\mu\text{g/g}$ in 5/50 (10%).^{5,6} However, there were no clinical correlations between FEL-1 level and the symptoms of steatorrhoea described by 20% of the patients.^{5,6} Larger studies are required to determine the true prevalence of PEI and the value of PERT in patients with these conditions.

Statement 2.5.3: Patients with coeliac disease on a gluten-free diet, but still experiencing diarrhoeal symptoms, should be investigated for PEI and treated

Page 4 of 12

with PERT if positive results are obtained. This should be reviewed at least annually as treatment may not need to be long term (Grade 1B; 100% agreement)

Comments

Studies suggest that approximately one-third of patients with coeliac disease who experience persistent symptoms (particularly diarrhoea) may have PEI.^{7,8} PERT may be of benefit for these patients;⁸ however, one study found that many had stopped taking PERT within 4 years of commencing treatment, suggesting that PEI is not permanent in patients with coeliac disease.⁹ Therefore, patients with coeliac disease established on a gluten-free diet but still experiencing diarrhoeal symptoms should be tested for PEI with FEL-1 and treated with PERT if positive. The test should be repeated at least annually as long-term treatment may not be required.

Statement 2.5.4: PEI should be considered in patients with IBS-D. The role of PERT in this group is not fully understood (Grade 2C; 95% agreement)

Comments

Two studies screened patients with functional bowel disorders for PEI using the FEL-1 test. In the first study, of 314 patients with diarrhoea-predominant irritable bowel syndrome (IBS-D), 19/314 (6.1%) had a FEL-1 level <100 µg/g stool, indicative of severe PEI. Following open-label treatment with PERT, there were significant improvements in abdominal pain ($p < 0.003$), stool frequency ($p < 0.001$) and stool consistency ($p < 0.001$).¹⁰ A subsequent study screened 218 patients with a range of functional gut symptoms and found that 10/218 (4.6%) had a FEL-1 level <200 µg/g stool and 2.3% had a FEL-1 <100 µg/g stool, with CP identified in two patients.¹¹ However, if those with IBS-D were considered alone, then 3/35 (8.6%) of patients had a low FEL-1 level, which is similar to the findings of Leeds, et al.¹⁰ No information was given regarding treatment in this study.¹¹ Given the high prevalence of IBS-D, routine FEL-1 testing of

these patients for PEI seems sensible, but more studies in this area are needed to strengthen this recommendation.

Statement 2.5.5: Patients with IBD and continued diarrhoeal symptoms should be investigated for PEI (Grade 2B; 100% agreement)

Comments

There appears to be an increased risk of developing CP in patients with inflammatory bowel disease (IBD) that increases over time.¹² The true frequency of PEI in patients with IBD is unknown, as clinically symptomatic PEI may be unrecognised and treated as a disease flare. Two studies reported a 14–22% prevalence of PEI in patients with IBD using the FEL-1 diagnostic test.^{13 14} However, this was possibly an underestimation, as FEL-1 levels may have been falsely reduced by watery stools caused by active disease, previous pancreatic damage or degradation of elastase by bacteria. Neither of these studies looked at the benefit of PERT in patients with abnormal FEL-1 levels. Some patients have continued diarrhoea despite mucosal improvement and improved inflammatory markers following standard treatment for IBD. In these circumstances, PEI should be considered.

Statement 2.5.6: Patients with HIV presenting with steatorrhoea, diarrhoea or weight loss should be investigated for PEI and offered PERT if positive results are obtained (Grade 2B; 88% agreement)

Comments

Gastrointestinal (GI) symptoms are common in patients with human immunodeficiency virus (HIV) infection, and autopsy studies have shown histological changes suggestive of exocrine pancreatic disease.¹⁵ The FEL-1 diagnostic test has indicated a prevalence of PEI of 23–54% in this patient population.^{16 17} PERT has been shown to reduce fat malabsorption and improve GI symptoms in patients with HIV infection and low FEL-1 levels.¹⁶⁻¹⁹ Most of these studies are small

and open-label and may have other confounders limiting their validity. Considering the impact and prevalence of fat malabsorption in patients with HIV, those with relevant symptoms should be tested for PEI and offered PERT if positive.

Statement 2.5.7: There may be an increased prevalence of PEI in patients with ALD, but the role of PERT in this group has not been examined (GPP; 89% agreement)

Comments

Identifying individuals with alcohol-related liver disease (ALD) and concomitant exocrine pancreatic disease is important, as nutrition in liver disease is crucial.²⁰ Despite this, there have only been a few small studies examining this relationship. Furthermore, the diagnostic tests used have varied between studies, resulting in a wide range of prevalence estimates. Two studies using direct intubation tests (involving endoscopic intubation of the pancreatic duct) showed that concomitant pancreatic disease occurred in 5/32 (15.6%) and 1/26 (3.8%) of patients with ALD, respectively.^{21 22} A study of 60 patients with liver cirrhosis, of which 35 were due to alcohol, showed that 18/60 (30%) had imaging changes consistent with CP.²³ Another study examining FEL-1 levels in patients with ALD reported PEI in 7% of patients.²⁴

None of these studies reported intervention with PERT and only two presented GI symptoms that might be relevant. This area is important, but there is a large gap in the data, meaning that the benefit of routine testing and treatment is unknown.

Table S2. Other causes of loose stools in patients with PEI despite PERT (see **table 5** in the main manuscript)

Cause	Investigation and treatment
SBBO	Investigated using a glucose hydrogen breath test. Ideally this should give values for both hydrogen and methane, but some centres only measure hydrogen. A rise of exhaled hydrogen of >20ppm is suggestive. This is not usually performed if the person has taken antibiotics in the last 4 weeks. Treatment for a positive result is antibiotics
BAM	Investigated using a SeHCAT scan, which requires two visits to the nuclear medicine department 7 days apart. Treatment for a positive result is with bile acid sequestrants
Infection	Investigated with a stool sample and usually treated with antibiotics
Coeliac disease	Consider a serum tissue transglutaminase and /or duodenal biopsy (biopsy not necessary if TTG > 10 x upper normal limit. ²⁵ Patient must be eating adequate gluten (equivalent to 4 slices of bread a day) for the 4 weeks prior to their test for a negative result to be accurate. Treatment for a positive result consists of a strict gluten-free diet
Lactase deficiency	Investigated with a breath test. Treatment for a positive result consists of removing intake of lactose from foods, drinks and medication
Other food intolerances	Investigated with an exclusion diet under the guidance of a specialist dietitian. Treatment involves avoidance of trigger foods
IBS-D	Can be treated with a low FODMAP diet under the guidance of a specialist dietitian.
No other cause identified	Anecdotally, some patients have fewer side effects and increased efficacy with one brand of PERT than another. Therefore, it is helpful for a patient to trial another brand of PERT if no other cause of the symptoms can be identified

BAM, bile acid malabsorption; IBS-D, diarrhoea-predominant irritable bowel syndrome; PERT, pancreatic enzyme replacement therapy; SBBO, small bowel bacterial overgrowth; SeHCAT, selenium homocholic acid taurine

REFERENCES

1. Rothenbacher D, Low M, Hardt PD, et al. Prevalence and determinants of exocrine pancreatic insufficiency among older adults: results of a population-based study. *Scandinavian journal of gastroenterology* 2005;40(6):697-704. doi: 10.1080/00365520510023116
2. Gullo L, Simoni P, Migliori M, et al. A study of pancreatic function among subjects over ninety years of age. *Pancreatology* 2009;9(3):240-4. doi: 10.1159/000212090 [published Online First: 2009/05/02]

3. Herzig KH, Purhonen AK, Rasanen KM, et al. Fecal pancreatic elastase-1 levels in older individuals without known gastrointestinal diseases or diabetes mellitus. *BMC geriatrics* 2011;11:4. doi: 10.1186/1471-2318-11-4 [published Online First: 2011/01/27]
4. Kauppi M, Kankaanpaa E, Kautiainen H. Exocrine dysfunction of the pancreas in patients with chronic polyarthritis. *Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases* 2001;7(3):166-9. [published Online First: 2006/10/14]
5. Griesche-Philippi J, Otto J, Schworer H, et al. Exocrine pancreatic function in patients with end-stage renal disease. *Clinical nephrology* 2010;74(6):457-64. doi: 10.5414/cnp74457 [published Online First: 2010/11/19]
6. Ventrucchi M, Cipolla A, Middonno M, et al. Impaired fecal elastase excretion in uremic pancreopathy. *Dig Dis Sci* 2000;45(11):2265-9. doi: 10.1023/a:1026487807555 [published Online First: 2001/02/24]
7. Abdulkarim AS, Burgart LJ, See J, et al. Etiology of nonresponsive celiac disease: results of a systematic approach. *Am J Gastroenterol* 2002;97(8):2016-21. doi: 10.1111/j.1572-0241.2002.05917.x [published Online First: 2002/08/23]
8. Leeds JS, Hopper AD, Hurlstone DP, et al. Is exocrine pancreatic insufficiency in adult coeliac disease a cause of persisting symptoms? *Alimentary pharmacology & therapeutics* 2007;25(3):265-71. doi: 10.1111/j.1365-2036.2006.03206.x [published Online First: 2007/02/03]
9. Evans KE, Leeds JS, Morley S, et al. Pancreatic insufficiency in adult celiac disease: do patients require long-term enzyme supplementation? *Dig Dis Sci* 2010;55(10):2999-3004. doi: 10.1007/s10620-010-1261-y [published Online First: 2010/05/12]

10. Leeds JS, Hopper AD, Sidhu R, et al. Some patients with irritable bowel syndrome may have exocrine pancreatic insufficiency. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2010;8(5):433-8. doi: 10.1016/j.cgh.2009.09.032 [published Online First: 2009/10/20]
11. Talley NJ, Holtmann G, Nguyen QN, et al. Undiagnosed pancreatic exocrine insufficiency and chronic pancreatitis in functional GI disorder patients with diarrhea or abdominal pain. *Journal of gastroenterology and hepatology* 2017;32(11):1813-17. doi: 10.1111/jgh.13791 [published Online First: 2017/03/24]
12. Chen YL, Hsu CW, Cheng CC, et al. Increased subsequent risk of inflammatory bowel disease association in patients with chronic pancreatitis: a nationwide population-based cohort study. *Current medical research and opinion* 2017;33(6):1077-82. doi: 10.1080/03007995.2017.1300143 [published Online First: 2017/03/10]
13. Maconi G, Dominici R, Molteni M, et al. Prevalence of pancreatic insufficiency in inflammatory bowel diseases. Assessment by fecal elastase-1. *Dig Dis Sci* 2008;53(1):262-70. doi: 10.1007/s10620-007-9852-y [published Online First: 2007/05/29]
14. Barthet M, Lesavre N, Desplats S, et al. Frequency and characteristics of pancreatitis in patients with inflammatory bowel disease. *Pancreatology* 2006;6(5):464-71. doi: 10.1159/000094564 [published Online First: 2006/07/19]
15. Chehter EZ, Longo MA, Laudanna AA, et al. Involvement of the pancreas in AIDS: a prospective study of 109 post-mortems. *AIDS (London, England)* 2000;14(13):1879-86. doi: 10.1097/00002030-200009080-00001 [published Online First: 2000/09/21]

16. Carroccio A, Di Prima L, Di Grigoli C, et al. Exocrine pancreatic function and fat malabsorption in human immunodeficiency virus-infected patients. *Scandinavian journal of gastroenterology* 1999;34(7):729-34. doi: 10.1080/003655299750025958 [published Online First: 1999/08/31]
17. Carroccio A, Fontana M, Spagnuolo MI, et al. Pancreatic dysfunction and its association with fat malabsorption in HIV infected children. *Gut* 1998;43(4):558-63. doi: 10.1136/gut.43.4.558 [published Online First: 1998/11/21]
18. Carroccio A, Guarino A, Zuin G, et al. Efficacy of oral pancreatic enzyme therapy for the treatment of fat malabsorption in HIV-infected patients. *Alimentary pharmacology & therapeutics* 2001;15(10):1619-25. doi: 10.1046/j.1365-2036.2001.01070.x [published Online First: 2001/09/21]
19. Price DA, Schmid ML, Ong EL, et al. Pancreatic exocrine insufficiency in HIV-positive patients. *HIV medicine* 2005;6(1):33-6. doi: 10.1111/j.1468-1293.2005.00263.x [published Online First: 2005/01/27]
20. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. *Journal of hepatology* 2019;70(1):172-93. doi: 10.1016/j.jhep.2018.06.024 [published Online First: 2018/08/27]
21. Angelini G, Merigo F, Degani G, et al. Association of chronic alcoholic liver and pancreatic disease: a prospective study. *Am J Gastroenterol* 1985;80(12):998-1003. [published Online First: 1985/12/01]
22. Hayakawa T, Kondo T, Shibata T, et al. Exocrine pancreatic function in chronic liver diseases. *Am J Gastroenterol* 1991;86(2):201-4. [published Online First: 1991/02/01]

23. Caradonna P, Costamagna G, Benedetti G, et al. Chronic pancreatitis prevalence in liver cirrhosis. Morphological and functional study. *The Italian journal of gastroenterology* 1996;28(2):91-4. [published Online First: 1996/02/01]
24. Aparisi L, Sabater L, Del-Olmo J, et al. Does an association exist between chronic pancreatitis and liver cirrhosis in alcoholic subjects? *World journal of gastroenterology : WJG* 2008;14(40):6171-9. doi: 10.3748/wjg.14.6171 [published Online First: 2008/11/06]
25. British Society of Gastroenterology. BSG Interim Guidance: COVID-19 specific non-biopsy protocol for those with suspected coeliac disease 2021] [updated 03/03/21; cited 2021]. Available from: <https://www.bsg.org.uk/covid-19-advice/covid-19-specific-non-biopsy-protocol-guidance-for-those-with-suspected-coeliac-disease/> accessed 04/05/2021.