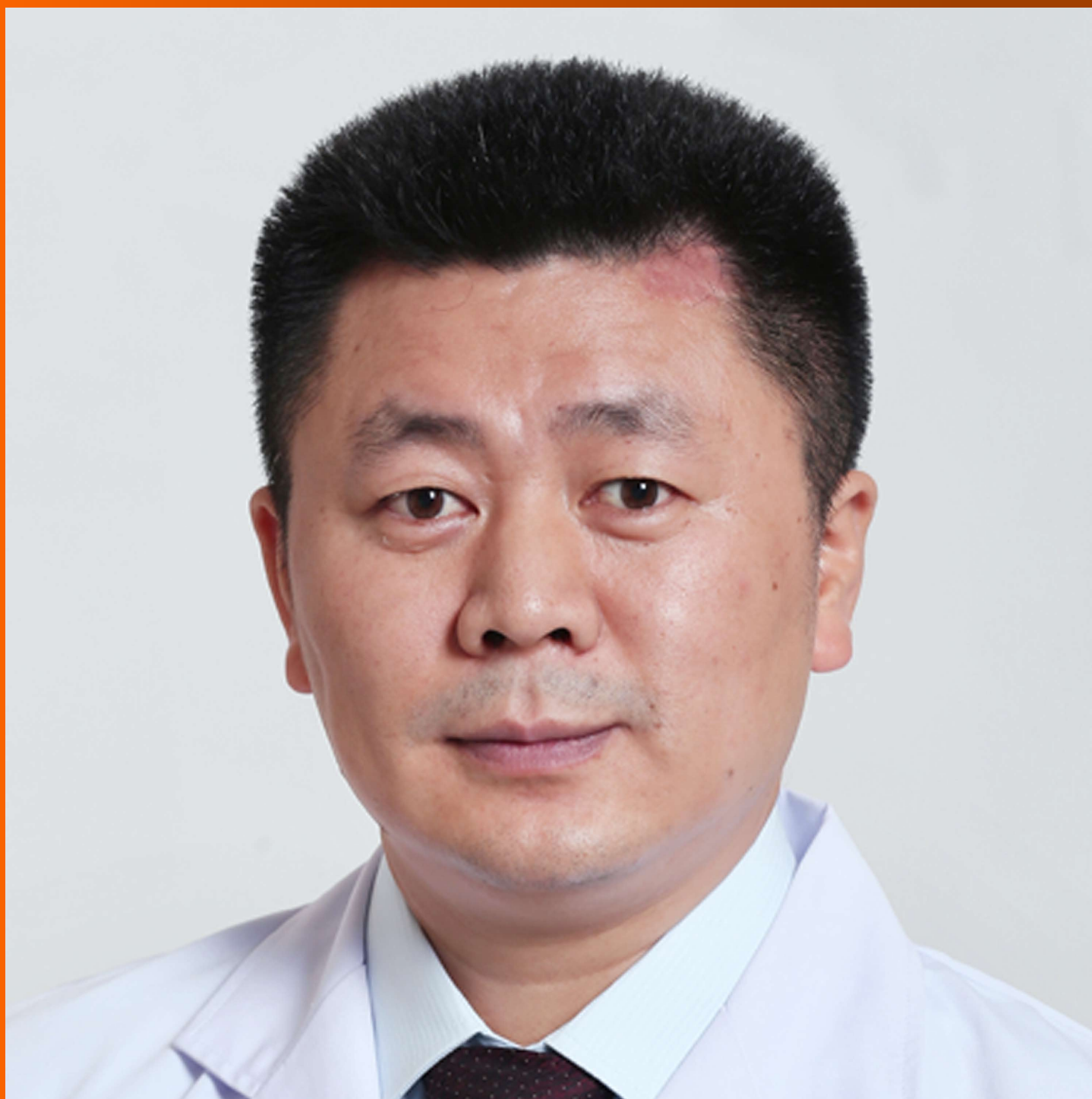


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**EDITORIAL**

- 39 Challenges in the management of pancreatic exocrine insufficiency  
*Shandro BM, Nagarajah R, Poullis A*

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## Challenges in the management of pancreatic exocrine insufficiency

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### Abstract

Pancreatic exocrine insufficiency (PEI) occurs when the insufficient secretion or function of pancreatic enzymes leads to maldigestion, most commonly as a result of chronic pancreatitis and pancreatic cancer. The condition is associated with significant morbidity and reductions in quality of life, even in milder forms. The challenges in approaching this condition include the non-specific presentation of mild to moderate PEI, and the lack of a convenient, accurate diagnostic test in this cohort. Classical symptoms appear late in the disease, and the diagnosis should be considered before steatorrhea develops. Direct pancreatic function tests are the reference standard for diagnosis, but are invasive and not widely available. The faecal elastase-1 (FE-1) stool test is widely available and has been shown to be as effective as the <sup>13</sup>C-mixed triglyceride breath test in more advanced disease. We recommend a pragmatic diagnostic approach that combines clinical history, assessment of nutritional status and measurement of FE-1. The critical first step is to consider the diagnosis. Once the diagnosis is confirmed, pancreatic enzyme replacement therapy should be initiated. The variety of enzyme preparations and recommended dosing regimens can present a challenge when selecting an adequate initial dose. Non-response should be actively sought and addressed in a systematic manner. This article discusses these challenges, and presents a practical approach to the diagnosis and management of PEI.

**Key words:** Pancreatic exocrine insufficiency; Chronic pancreatitis; Steatorrhea; Pancreatic function tests; Pancreatic enzyme replacement therapy

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**Core tip:** Pancreatic exocrine insufficiency (PEI) is common, and the prevalence is likely to increase in line

with global trends in associated conditions (notably increasing age and diabetes mellitus). The classical symptom of steatorrhoea is a late presentation of PEI. The diagnosis should be considered far earlier, based on risk factors and clinical history. A current, pragmatic approach to diagnosis combines clinical history, assessment of nutritional status and measurement of faecal elastase-1. Treatment with pancreatic enzyme replacement therapy (PERT) is safe and effective. PERT must be adequately dosed, monitored, and optimized to ensure its benefits are realized.

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## INTRODUCTION

Pancreatic exocrine insufficiency (PEI) is defined by insufficient secretion or function of pancreatic enzymes or sodium bicarbonate for normal digestion. It is commonly caused by a reduction in functioning pancreatic tissue or ductal disease, such as in chronic pancreatitis and pancreatic malignancy. It can also result from reduced enterohormonal stimulation of the pancreas in severe duodenal mucosal disease, and from anatomical changes following gastrointestinal surgery<sup>[1]</sup>.

The prevalence of PEI in the general population has not been established, and is problematic owing to a lack of a suitable screening test. It is accepted that the prevalence of PEI increases with age, and it is estimated to be as high as 11.5%-20% in apparently healthy older individuals<sup>[2,3]</sup>. Studies of selected populations estimate the prevalence of PEI to be 85% in advanced chronic pancreatitis, 50%-100% in inoperable pancreatic cancer, 56%-98% following pancreaticoduodenectomy, 85% in cystic fibrosis, 30% in coeliac disease, and 40% in diabetes mellitus<sup>[1]</sup>. The aging population and increasing incidence of diabetes mellitus worldwide suggest that PEI will be a more commonly encountered clinical problem in the future.

There are multiple diagnostic tests for PEI, and a balance between diagnostic accuracy and feasibility has not yet been achieved, particularly for milder disease. The cornerstone of treatment is pancreatic enzyme replacement therapy (PERT), but studies suggest that treatment is sub-optimal in more than half of patients<sup>[4]</sup>.

This narrative article will explore the challenges that arise in the diagnosis and management of PEI.

## DIAGNOSIS OF PANCREATIC EXOCRINE INSUFFICIENCY

PEI initially presents with symptoms of bloating, excessive

flatulence, abdominal discomfort and diarrhoea, which are common to many other gastrointestinal conditions<sup>[1]</sup>. The classical symptoms of steatorrhoea and weight loss develop late in the course of PEI, when the secretion of pancreatic lipase is less than 10% of normal<sup>[5]</sup>. However, even patients with mild or moderate PEI are at risk of nutritional deficiencies, particularly of fat-soluble vitamins, and their consequences, including osteoporosis, renal insufficiency, and reduced quality of life<sup>[6,7]</sup>. As such, early consideration of PEI, based on risk factors and non-specific symptoms, is vital.

### Direct Tests

The gold standard test for the diagnosis of PEI is said to be direct pancreatic function testing, where pancreatic secretions are measured in the duodenum or pancreatic duct following the administration of a secretagogue. Although direct tests are considered the most sensitive tests for PEI, multiple techniques exist and there is a lack of standardisation across the few centres that offer them. In addition, direct pancreatic function testing is expensive, invasive, and technically challenging<sup>[6]</sup>. As a result, invasive direct tests lack clinical application.

There has been interest in non-invasive direct pancreatic function testing using secretin-stimulated magnetic resonance cholangiopancreatography (S-MRCP). One study comparing this technique to the intra-ductal secretin test demonstrated a sensitivity of 72% and specificity of 87%<sup>[8]</sup>, whilst another comparing S-MRCP to the secretin endoscopic pancreatic function test found 100% sensitivity and specificity<sup>[9]</sup>. Both studies are limited by small patient numbers. There is a lack of robust evidence to recommend this as a single diagnostic test for PEI, but it can provide additional information on pancreatic exocrine function whilst assessing the structure of the pancreas.

### Indirect tests

**Quantitative faecal fat estimation:** The 72-h faecal fat test is considered the gold standard for the diagnosis of fat malabsorption, and can also be used to assess the adequacy of PERT. Stool is collected for 72 h whilst the patient consumes 100 g of fat per day. Steatorrhoea is defined by > 7 g of fat per 100 g of stool per day, or a calculated co-efficient of fat absorption < 90%<sup>[10]</sup>. However, the test is not specific for PEI, and false negatives may occur where there is poor adherence to, or reporting of, dietary fat intake. The test is time consuming and unpleasant for both the patient and laboratory staff. In our experience few centres offer this test routinely.

**<sup>13</sup>C-mixed triglyceride breathe test:** The use of stable isotope breath testing of metabolic and physiological function is well established in gastroenterology. The <sup>13</sup>C-mixed triglyceride (<sup>13</sup>C-MTG) breath test is a study of the digestion of an isotope-labelled fat meal that has emerged as an indirect measure of pancreatic exocrine



function that is accurate, simple, repeatable, and non-invasive. Studies comparing the  $^{13}\text{C}$ -MTG breath test to endoscopic secretin studies and 72-h faecal fat measurement demonstrate a sensitivity of 90%-100% and a specificity of 90%-92%<sup>[11,12]</sup>. An additional strength is that it can be used to assess response to treatment, with normalisation of  $^{13}\text{C}$ -MTG breath test results correlating with weight gain and the normalisation of faecal fat and nutritional deficiencies<sup>[13]</sup>.

The length of time over which excreted  $\text{CO}_2$  is measured, the constituents of the test-meal, and physical exercise may affect results<sup>[14]</sup>. An attempt to simplify the  $^{13}\text{C}$ -MTG breath test showed that when cumulative  $\text{CO}_2$  excretion is measured over less than 4 h the test loses its specificity, although it remains highly sensitive<sup>[15]</sup>. The test may generate false positives in patients with steatorrhoea of non-pancreatic origin, such as those with severe duodenal mucosal disease<sup>[16]</sup>. These limitations can be addressed by standardising test protocols and excluding duodenal mucosal disease as part of a considered diagnostic work-up for patients with diarrhoea. The main limitation of the  $^{13}\text{C}$ -MTG breath test is that it is more costly and time-consuming than alternatives, namely faecal elastase-1 (FE-1), without convincing evidence of superiority. Furthermore, it is not yet widely available, having not been commercialised in many countries at time of publication. Therefore in many countries it cannot yet be incorporated into clinical practice.

**Faecal elastase-1:** FE-1 measures a protease, secreted only by the pancreas, that has been shown to be stable during intestinal transit and correlate well with duodenal levels of lipase and bicarbonate<sup>[17]</sup>. An FE-1 value of < 200  $\mu\text{g/g}$  is used as a conventional cut-off for diagnosing PEI, but the result should be viewed as a continuum.

A recent meta-analysis demonstrated a pooled sensitivity of 77% and specificity of 88%, when compared to the secretin stimulation test, and 96% and 88% when compared to quantitative faecal fat estimation<sup>[18]</sup>. It compares favourably with, and has largely replaced, previous indirect tests such as faecal chymotrypsin estimation and the pancreolauryl test<sup>[19,20]</sup>. Concerns over the lack of sensitivity in mild PEI persist, however FE-1 was found to be more sensitive and specific than the  $^{13}\text{C}$ -MTG breath test in a direct comparison study that included patients with both mild and severe PEI<sup>[20]</sup>.

FE-1 is measured from a single, solid stool sample, and does not degrade if the sample is stored for several days<sup>[17]</sup>. As a result it is a cheap and practical test, and has been adopted as the primary diagnostic test for PEI in most centres. FE-1 is not affected by PERT therefore it cannot be used to monitor response to therapy<sup>[21]</sup>.

**Assessment of nutritional status:** Malnutrition is common in PEI, though non-specific, and established markers of malnutrition can be used as part of the

diagnostic approach<sup>[6]</sup>. Anthropometric measurements such as body mass index and muscle stores are lower in patients with PEI than in controls<sup>[22]</sup>. Vitamin D deficiency is found in 53% of patients with PEI<sup>[23]</sup>, and a retrospective study found that hypomagnesaemia detects PEI with a sensitivity of 88% and specificity of 66%<sup>[24]</sup>.

### **Recommended approach**

Our current, pragmatic approach is to combine clinical history, assessment of nutritional status, tests to exclude other causes of malabsorption, and FE-1 to determine the likelihood of PEI in an individual patient. Imaging to assess the structure of the pancreas and exclude pancreatic carcinoma should be carried out in all patients diagnosed with PEI in adulthood. Where it is available, S-MRCP is the logical imaging modality of choice, given the additional functional information gained<sup>[6]</sup>.

## **MANAGEMENT OF PANCREATIC EXOCRINE INSUFFICIENCY**

The overall aim of treating PEI must be to normalise digestion to improve the quality and longevity of life. PERT is the cornerstone of the management of PEI. It has been shown to improve weight, reduce faecal fat excretion, ameliorate abdominal pain and improve quality of life, without significant side effects<sup>[25]</sup>. Although its impact on long-term survival in chronic pancreatitis has not been studied, PERT has been shown to improve survival rates in patients with unresectable pancreatic cancer and following pancreatic surgery<sup>[26,27]</sup>.

Despite these benefits, evidence suggests that clinicians are not initiating treatment often enough, nor replacing enzymes adequately. A recent study showed that only 21% of patients with pancreatic cancer received PERT, despite 70% reporting symptoms consistent with fat maldigestion<sup>[28]</sup>. A Northern European cross sectional survey of patients receiving PERT found 68% had steatorrhoea and 39% had weight loss. Nearly half were needlessly restricting their fat intake and only 36% had seen a dietitian<sup>[4]</sup>. Similar findings emerged from a Dutch National survey<sup>[29]</sup>.

This suggests that there is a great deal of room for improvement in our management of PEI, particularly in terms of initiating and optimising PERT. Challenges in achieving this include the availability of multiple different enzyme preparations, the need to individualise dosing and timing of PERT, and uncertainty about how to monitor and optimise treatment in non-responders.

### **Pancreatic enzyme replacement therapy**

**Enzyme preparations:** An effective PERT preparation should intersperse well with chyme, resist denaturation by gastric juices, empty from the stomach simultaneously with nutrients, and release enzymes quickly in the proximal small intestine.

Conventional (uncoated) preparations are vulnerable

to denaturing by gastric acid. However, most modern preparations are pH-sensitive, enteric-coated mini-microspheres, enclosed within a gelatine capsule shell. The enteric coating of the microspheres is acid resistant and dissolves in the duodenum at a pH of around 5.5.

There are marked differences in the rate of release of lipase between preparations *in vitro*, but little clinical data supports any specific preparation over another<sup>[30,31]</sup>. The size of the microspheres is important, however, as this determines the rate at which they empty into the small bowel. Spheres of 2.4 and 3.2 mm diameter empty more slowly than 1 mm spheres, and may not enter the small bowel at the same time as ingested food<sup>[32]</sup>.

In current practice, enteric-coated microspheres or mini-microspheres of < 2 mm in size are the preparation of choice<sup>[6]</sup>.

**Dosing:** If chyme stays within the duodenum for four hours, physiological lipase output is between 480000 and 960000 units after a standard meal<sup>[33]</sup>. As steatorrhoea only occurs when lipase output falls to < 10% of normal<sup>[5]</sup>, the minimum number of lipase units required for normal digestion would be 24000 to 48000<sup>[33]</sup>. However, exogenous lipase is only one third as effective endogenous lipase<sup>[6]</sup>, probably owing to partial denaturing by gastric acid and late release in the distal small bowel<sup>[33]</sup>.

There is a lack of consensus on the optimum dose of PERT. Randomised controlled trials have shown that PERT is effective at doses of 72000-75000 IU with main meals, and 36000-50000 IU with snacks<sup>[34,35]</sup>. Recent European guidelines recommend a minimum starting dose of 40000-50000 IU with main meals for adults with chronic pancreatitis, and half that dose with snacks<sup>[6]</sup>. The Australasian Pancreatic Club suggests a starting dose of 25000-40000 lipase units with food<sup>[36]</sup>.

For adults with cystic fibrosis, Australia and New Zealand guidelines recommend PERT dosing based on grams of dietary fat: 500-4000 lipase units per gram of fat consumed<sup>[37]</sup>. This equates to 12000-92000 lipase units for a 600-calorie meal in which 35% of calories are from fat. The ESPEN-ESPGHAN-ECFS guidelines for cystic fibrosis suggest PERT supplementation in lipase units per kilogram body weight per meal. They propose an initial dose of 500 lipase units/kg/meal<sup>[38]</sup>. This equates to approximately 30000 lipase units for a 60 kg adult eating a normal meal. The requirement to quantify dietary fat requires highly motivated patients and adds to the challenge of managing PEI in this population.

A patient's PERT requirements vary according to aetiology of PEI, residual pancreatic function and dietary intake, and may change over time. Larger or fattier meals will require more enzymes than a small, low fat one so the dose of PERT should reflect this<sup>[39]</sup>. Clinical experience demonstrates that a doubling or tripling of initial dose is needed in some patients, however, robust evidence is lacking<sup>[6]</sup>. The need for an individualised approach to PERT may explain the discrepancy between

dosing guidelines. Where there is consensus is on the need to review and titrate PERT according to the degree of malabsorption<sup>[39]</sup>.

We recommend that PERT be initiated at 50000-75000 lipase units with meals and 25000-50000 lipase units with snacks, and that dosing is reviewed regularly. In patients with pancreatic cancer it is prudent to initiate a dose at the upper end of the recommended range, as prompt, adequate PERT has been shown to improve survival and quality of life<sup>[26,27]</sup>.

**Timing:** The efficacy of PERT requires the mixing of enzymes with chyme, and their synchronised arrival in to the duodenum. The timing of PERT administration therefore influences clinical outcomes. A randomised three way cross over study evaluated the effect of giving enteric-coated mini-microspheres before, during, or after meals in 24 patients with chronic pancreatitis. The percentage of patients who achieved normal fat digestion was highest in patients taking PERT during meals (63%), compared to before or after meals (50% and 54%)<sup>[40]</sup>. Therefore it is recommended to give PERT during meals, distributed evenly across the meal if more than one capsule is taken<sup>[6,25,39]</sup>.

**Side effects:** PERT is generally well tolerated<sup>[41]</sup>. Fibrosing colonopathy is a much discussed but rarely seen complication that has been reported in children with cystic fibrosis using large doses of PERT<sup>[42-45]</sup>. As a result it is recommended that enzyme dose does not exceed 10000 lipase units per kg per day<sup>[46,47]</sup>. Assuming three meals and two snacks a day, this equates to 150000 lipase units with meals and 75000 lipase units with snacks for a 60 kg adult.

**Religious or ethical constraints:** All PERT preparations available in the United Kingdom are of porcine origin. This challenges individuals from certain religions, including Judaism and Islam, as well as vegetarians and vegans. Where religious or ethical beliefs are at odds with PERT, our experience is of non-adherence. Religious patients can be referred to their religious leaders for guidance. Imams or Rabbis usually grant special exemptions where no suitable alternative medication exists and non-adherence poses a threat to health. A novel, non-porcine, PERT is in development, which should improve adherence in these populations<sup>[48]</sup>.

**Monitoring response:** Commencement of PERT is associated with a relatively quick improvement in symptoms of maldigestion, such as steatorrhoea and weight loss. However, adequacy of PERT should not be assessed based on clinical signs and symptoms alone, as serum markers of nutrition can be low in asymptomatic patients<sup>[49]</sup>. Therefore response to PERT should also be assessed by normalisation of serum nutritional markers, including fat soluble vitamins, retinol-binding protein, albumin, pre-albumin and minerals/trace elements

(including serum iron, zinc and magnesium)<sup>[6,24]</sup>.

### Management of non-response

An inadequate response to PERT should be assessed in a systematic manner. The expiry date and mode of storage of PERT preparations should be checked. Patient compliance should be assessed, particularly regarding the timing of PERT in relation to meals and snacks. Where compliance is poor, a higher strength capsule may help to reduce the pill burden. A dietary history may identify opportunities to individualise PERT according to the size and fat content of each meal, which may be more effective than a fixed dose regimen.

If these factors have been addressed, consider increasing the enzyme dose (by two or three times, to a maximum of 10000 lipase units per kg body weight)<sup>[6]</sup>. Failing this, adjunctive acid suppression therapy may help.

A significant proportion of patients with PEI demonstrate an inadequate response to enteric-coated enzyme therapy alone<sup>[50]</sup>. One possible explanation is reduced pancreatic bicarbonate secretion, impairing neutralisation of acidic chyme<sup>[51]</sup>. If the intra-duodenal pH is lower than 5.0, the enteric coating will not dissolve on time and enzyme release will happen in the distal small bowel<sup>[52]</sup>.

The use of acid suppression with enteric-coated PERT may increase gastric pH and enhance PERT efficacy. In a prospective, open, comparative study, 21 patients with newly diagnosed PEI were treated with enteric-coated mini-microspheres (40000 IU) three times a day, with the addition of esomeprazole after 3 mo. <sup>13</sup>C-MTG breath tests normalised in 57% of patients with PERT monotherapy. In non-responders, the addition of esomeprazole normalised fat digestion in an additional 29% of participants<sup>[50]</sup>.

Although data is of only moderate quality and large multicentre trials are still required, the combined use of acid suppression and PERT is considered appropriate when the response to PERT alone is suboptimal<sup>[6,25,37-39]</sup>. It should be noted that there is limited evidence to support adjuvant acid suppression in PEI caused by cystic fibrosis<sup>[53-56]</sup>.

If maldigestion does not respond to patient education, optimisation of PERT dose and adjuvant acid suppression, then other causes, such as small intestinal bacterial overgrowth, bile acid malabsorption, coeliac disease, inflammatory bowel disease, and lactose intolerance should be investigated and treated<sup>[6,37,39]</sup>.

Quantitative faecal fat estimation or the <sup>13</sup>C-MTG breath test can be used to evaluate adequacy of PERT in problematic non-responders, although neither test is widely available<sup>[6]</sup>.

### Management of diet and lifestyle

**Dietary modification:** Patients with PEI may self-restrict fat intake to minimise symptoms. Fats and oils are convenient energy sources and are especially

useful for PEI patients, who may have raised energy requirements and/or poor appetite. Reduced fat diets are not recommended for people with PEI<sup>[6]</sup>. A low-fat diet may further compromise endogenous enzyme secretion<sup>[57]</sup>, and was associated with poorer outcomes in children with cystic fibrosis compared to a normal diet with adequate PERT<sup>[58]</sup>. Medium-chain triglycerides, which do not require bile or lipase for absorption, do not seem to offer an advantage over a long-chain fat if PERT is used<sup>[59]</sup>.

There is widespread agreement that with adequate PERT, patients should be able to maintain a normal diet. A specialist dietitian can help prevent needless dietary restrictions related to patient anxiety about maldigestion-related symptoms.

**Lifestyle modification:** Referrals for alcohol cessation are recommended. Alcohol consumption is the most important risk factor for chronic pancreatitis<sup>[60]</sup>, with a three-fold increase in the risk of transitioning from acute to chronic pancreatitis in patients with ongoing alcohol consumption<sup>[61]</sup>. Smoking is an independent risk factor for both acute and chronic pancreatitis, and may produce a synergistic effect with alcohol<sup>[60]</sup>. Therefore, all patients should be counselled to abstain from smoking and consuming alcohol.

### Recommended approach

Our practice is to use an initial dose of 50000-75000 lipase units with meals and 25000-50000 lipase units with snacks, administered over the duration of the meal, rather than just at the start. A normal diet is recommended, as is the cessation of smoking and alcohol consumption. In non-responders, patient education, flexible dosing of PERT, increasing the dose of PERT, and adjunctive acid suppression can be attempted, and achieves a response in most patients.

## CONCLUSION

PEI is an important clinical entity that is often under recognised and undertreated. The symptoms of PEI generally appear late in the disease course and are non-specific. Clinically important nutritional deficiencies precede symptoms and contribute to significant morbidity and mortality. Unfortunately there is no widely available non-invasive test that is accurate in the early stages of PEI, and this should be a priority for future research.

Invasive direct pancreatic function tests are the reference standard, especially in mild PEI, but are unavailable outside of research centres. A combination of clinical history, nutritional assessment and measurement of FE-1 is a pragmatic but imperfect approach.

In PERT we have an effective and safe treatment for PEI that improves symptoms and nutritional status in the majority patients, and improves survival in patients with pancreatic carcinoma. Although the variety of PERT preparations and recommended dosing regimens can



be intimidating to practising clinicians, international consensus is now emerging.

There are opportunities for further research and developments in diagnostics that should be explored, but first we must do the simple things well. This is a condition with significant morbidity that has an effective treatment. The critical step in making the diagnosis of PEI is to consider it.

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