Clinical Guideline

THE PRESCRIBING AND MONITORING OF PANCREATIC ENZYME REPLACEMENT THERAPY (PERT)

SETTING Trustwide

FOR STAFF Staff who prescribe or advise on PERT

PATIENTS Adult inpatient and outpatients

Background

Pancreatic exocrine insufficiency (PEI) is defined as the primary or secondary disturbance of exocrine pancreatic function leading to reduced secretion of digestive enzymes and subsequent maldigestion of nutrients. Maldigestion is associated with malabsorption of nutrients which can lead to malnutrition.

Pancreatic enzyme replacement therapy (PERT) is central to the management of PEI as this can improve digestive function and prevent the clinical consequences of PEI.

PERT preparations contain varying amounts of lipase, amylase and protease which digest fat, carbohydrate and protein. There are a range of PERT preparations available (see appendix A) all of which are dosed by the minimum amount of lipase they contain. The active component of all preparations is Pancreatin which is derived from porcine pancreas gland.

This clinical guideline provides advice on appropriate prescribing and monitoring of PERT in both the inpatient and outpatient settings.

Causes of PEI

PEI can be caused by any condition that disrupts normal intraluminal enzyme activity to the point at which normal digestion of nutrients is no longer possible. This is commonly associated with:

- Reduced functional capacity of the pancreas to synthesise digestive enzymes due to loss of or injury to pancreatic parenchyma
- Impaired delivery of enzymes to the duodenum due to pancreatic ductal abnormalities
- Reduced stimulation of pancreatic secretions due to post-prandial asynchrony

Diagnosis

Diagnosing and assessing the severity of PEI in clinical practice can be difficult and the most appropriate approach varies according to the clinical condition. In the UK a reliable diagnostic test is lacking and it can be difficult to diagnose PEI with certainty.

In clinical practice a combination of clinical history, examination, pancreatic function tests and pancreatic imaging (when available) can inform a diagnosis of PEI. Each information source should be considered rather than a single measure in isolation to diagnose PEI. Advice on the assessment and interpretation of these areas is discussed below.

Clinical signs

The clinical signs associated with PEI are varied and often non-specific. No one symptom can be used to accurately diagnose PEI but a collection of symptoms can be highly suggestive of PEI.

Symptoms can include;

- Malnutrition (low BMI, weight loss), fat soluble vitamin deficiency (A, D, E, K), bone disease such as early onset osteoporosis, fatigue
- GI disturbances – bloating, flatulence, abdominal discomfort
- Steatorrhoea (high faecal fat content). Stools may appear loose, large volume, frequent, light in coloured, foul smelling, difficult to flush away or leave a greasy film in the toilet.

When assessing the clinical signs of PEI it is important to consider the following points

- Faecal fat losses can be significant without any overt symptoms of steatorrhoea
- Steatorrhoea will only occur if sufficient dietary fat is consumed. The avoidance of fat containing foods is common in patients with PEI as tolerance is likely to be poor.
- PEI is not the only condition that can cause these clinical signs so other potential causes should also be considered.

Clinical history

Conditions significantly affecting the pancreas or upper GI tract are known to have a high incidence of PEI. Cystic fibrosis, severe necrotising pancreatitis, chronic pancreatitis with calcification, pancreatic cancer, pancreatic resection and upper GI surgery including total gastrectomy and gastrojejunostomy carry a high probability of PEI.

Pancreatic Function Tests

Faecal elastase-1 (FE-1) is the most widely used pancreatic function test in the UK. Elastase is a protein secreted by the pancreas which passes through the GI tract unchanged. FE-1 concentration from a stool sample can be used as a marker of pancreatic enzyme secretion.

FE-1 key points

- Has good sensitivity in diagnosis severe PEI
- It is less reliable in diagnosing mild-moderate PEI
- It is a measure of pancreatic secretion not digestion. Maldigestion due to inadequate enzyme activity or mixing with nutrients can still occur despite adequate enzyme secretion
- Timing from sample submission to test report can take up to 4-6 weeks
- False positives are possible with diarrhoea due to dilution
- Taking pancreatic enzymes does not affect the validity of a FE-1 test

Faecal elastase-1 values:

Normal	>200 µg/g stool
Mild PEI	100-200 µg/g stool
Severe PEI	<100 µg/g stool

Imaging

Pancreatic imaging such as CT, MRI, EUS and MRCP can be used to visualise and assess the pancreas. Significant structural changes such as pancreatic atrophy and ductal abnormalities can infer a high probability of PEI. It is rarely appropriate to carry out imaging exclusively for the diagnosis of PEI but many patients with PEI will have had previous pancreatic imaging.

Aim of PERT

The aim of PERT is to restore digestion, relieve the symptoms of PEI and prevent or treat malnutrition. Effective digestion requires PERT to remain active and mix thoroughly with food to allow the digestive enzymes to act.

Prescription

The key to effective PERT is taking the correct dose at the correct times. A sufficient quantity of digestive enzyme needs to mix thoroughly with food in the GI tract to achieve effective digestion. A number of issues should be considered when prescribing PERT.

Dose

- The optimal PERT dose can be difficult to ascertain and usually requires ongoing review and adjustment to achieve. Doses should start at the lower end of what is expected to have a clinical impact and be titrated up until effective digestion is achieved.
- Minimum starting doses of 50,000 units lipase per meal and 25,000 units lipase per snack are recommended. In cases where severe PEI are anticipated (such as following a Whipple's resection) a higher starting dose of 75000 units lipase per meal and 25000-50000 units lipase per snack are recommended.
- There is no maximum dose for PERT. Doses should be titrated up until optimal digestion is achieved. This guideline recommends that if optimal digestion has not been achieved with a dose of 10,000 units lipase/kg body weight that clinicians consider investigating for other potential causes of maldigestion/malabsorption before increasing the dose further.
- Consider using high strength preparations such as Creon 25,000 or Nutrizyme 22 to minimise pill burden. Appendix A details the available pancreatin preparations.

Timing

- PERT should usually be administered just prior to eating to allow it to mix with food
- If taking more than 2 capsules spread the dose throughout the meal or snack
- PERT should be taken with all food and fluid that contain fat. This includes milky drinks and any supplement drinks. Fat free food and drink is unlikely to need PERT for digestion.
- Prescribe a regular dose with meals and a PRN dose with snacks
- Nutritional intake will often vary day to day and so patients should have the flexibility to adjust the dose and timing depending on a variable intake

Other Considerations

- Patients should be informed that pancreatin is of porcine origin. This can be particularly important for patients who choose to avoid animal and pig derived products. Currently there is no non-porcine derived alternative.
- Adjunct therapy. In PEI pancreatic bicarbonate secretions also fall leading to reduced buffering of acidic gastric chyme and a lower pH in the small bowel which inhibits the action of PERT. Acid suppression should therefore be considered to improve the action of PERT. A twice daily dose (morning and evening) is often recommended to optimise therapy over a 24 hour period. e.g Omeprazole 20mg – 40mg po bd

Monitoring and adjustment

Following the initiation of PERT the monitoring of nutritional status and GI function are important to guide further adjustments to PERT, optimise therapy and inform the need for further investigations. In patients with longstanding fat malabsorption clinicians should consider monitoring fat soluble vitamins (A, D and E) for deficiency. PEI is associated with an increased incidence of osteoporosis so clinicians should also consider monitoring bone mineral density. Appendix B provides an algorithm to guide clinicians in monitoring and adjusting PERT.

Review

PEI usually develops due to irreversible changes to the pancreas and a permanent loss of pancreatic exocrine function and as such PERT is required long term. Some conditions however such as acute pancreatitis or reversible pancreatic ductal abnormalities can cause PEI but with pancreatic exocrine function recovering to some degree in the months and years following an acute episode. In such cases repeat pancreatic function tests and/or short term trial without PERT can be useful in assessing PEI and the need for ongoing PERT. This should always be carried out under the supervision of an experienced clinician, dietitian or clinical nurse specialist.

In patients who are undergoing palliative care who have PEI the symptomatic effects of PERT should be considered in conjunction with the patient. PERT often carries a heavy pill burden but may have utility in managing troubling GI symptoms after optimising nutritional status ceases to be an objective. Liaising with the local palliative care services can be useful in these instances.

Enteral tube feeding

The management of PEI in enteral feeding is covered in a separate clinical guideline on the DMS entitled *Administering PERT via an Enteral Feeding Tube.*

RELATED DOCUMENTS	British National Formulary 78. September 2019 - March 2020 Administering Pancreatic Enzyme Replacement Therapy (PERT) via an Enteral Feeding Tube
SAFETY	PERT may increase the chance of having a rare bowel disorder called fibrosing colonopathy. Any unusual or severe stomach pain; frequent or abnormal bowel movements; bloating; trouble passing stool; nausea; vomiting; diarrhoea; worsening of gout; painful, swollen joints; trouble with breathing; skin rashes; or swollen lips should be reported to a healthcare professional. Activation of PERT within the mouth can cause oral irritation. Preparations should not be crushed, chewed or sprinkled over a meal.
QUERIES	Tom Lander, Senior Dietitian Ext 27360 / Bleep 2250 On call pharmacist via the UH Bristol switchboard

Appendix A: Pancreatin preparations

List of Pancreatin preparations covered by this protocol	Details
Creon 10000 (Abbott Healthcare)*	Capsules containing enterically coated granules of pancreatin (pork) providing protease (600 units), lipase (10000 units) and amylase (8000 units).
Creon 25000 (Abbott Healthcare)*	Capsules containing enterically coated granules of pancreatin (pork) providing protease (1000 units), lipase (25000 units) and amylase (18000 units).
Creon 40000 (Abbott Healthcare)*	Capsules containing enterically coated granules of pancreatin (pork) providing protease (1600 units), lipase (40000 units) and amylase (25000 units).
Creon Micro (Abbott Healthcare)	Gastro-resistant granules of pancreatin (pork) providing protease (200 units), lipase (5000 units) and amylase (36000 units) per 100mg.
Nutrizym 10 (Merck Sorono)	Capsules containing enterically coated minitablets of pancreatin (pork) providing protease (500 units), lipase (10000 units) and amylase (9000 units).
Nutrizym 22 (Merck Sorono)	Capsules containing enterically coated minitablets of pancreatin (pork) providing protease (1100 units), lipase (22000 units) and amylase (19800 units).
Pancrex V powder (Paines and Byrne)*	Powder, pancreatin (pork) providing protease (1400 units), lipase (25000 units) and amylase (30000 units) per gram.
Pancrease HL (Janssen)	Capsules containing enterically coated minitablets of pancreatin (pork) providing protease (1250 units), lipase (25000 units) and amylase (22500 units).

* Preparations available on UH Bristol formulary

Note: The availability of specific PERT preparations can vary at any given time. The pharmacy department can be contacted to clarify availability.

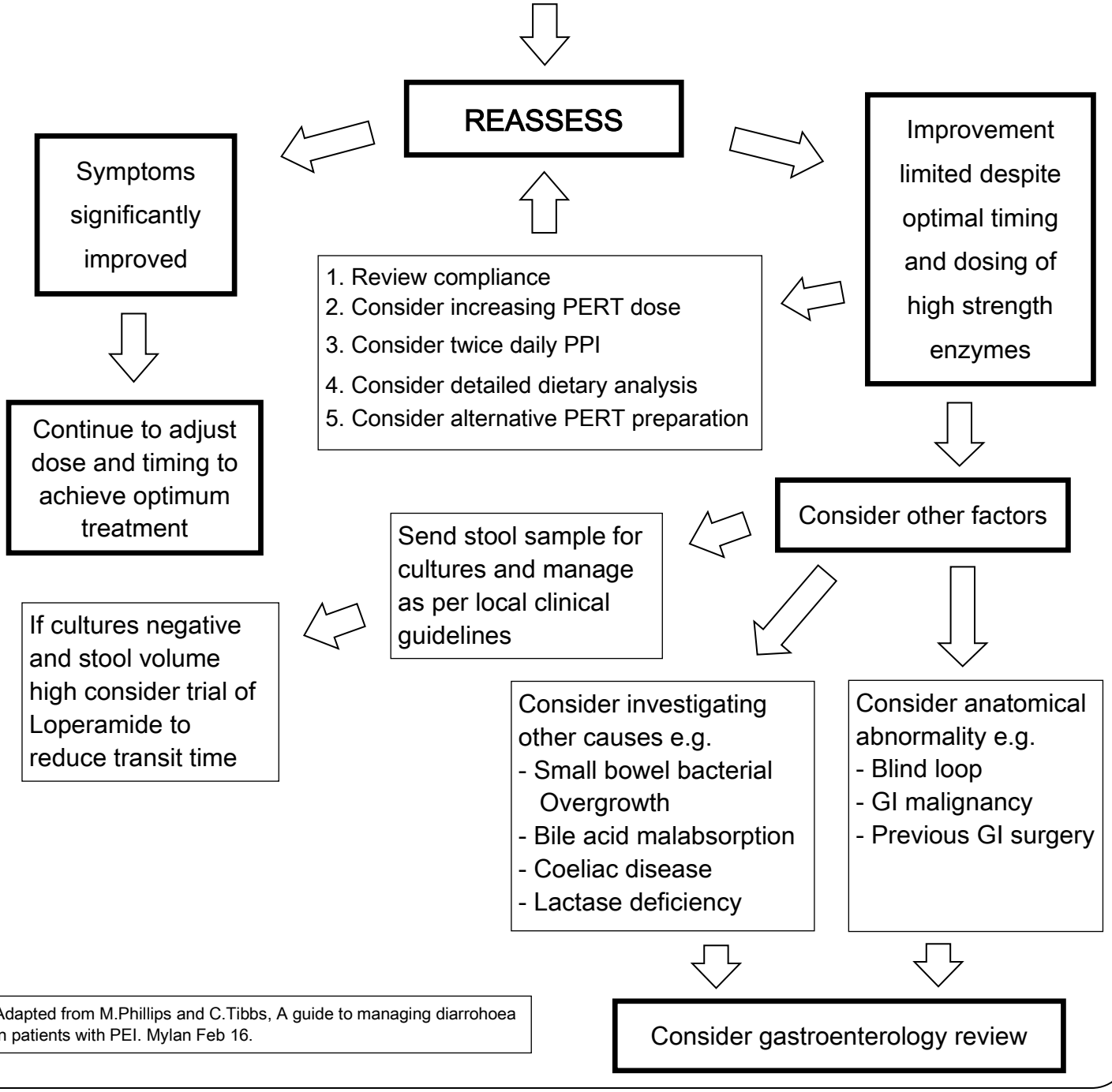
Appendix B: Managing Pancreatic Enzyme Replacement Therapy - A guide for clinicians

Aim of Treatment

- Normalise bowel motions for patient - colour, frequency, volume, consistency, urgency
- Minimise nutritional losses and malnutrition as a result of maldigestion and malabsorption

Commence Pancreatic Enzyme Replacement Therapy (PERT)

- Minimum starting doses 50,000units lipase/meal and 25,000 units lipase/snack
- Provide education on timing, dosing and adjustment of enzyme supplements
- Consider prescription for acid suppression
- Consider checking fat soluble vitamin levels(particularly if fat malabsorption is longstanding)
- If the number of capsules taken with meals exceeds 2 consider
  - using higher strength capsules to improve compliance and QoL
  - spread dose throughout meal(e.g. one capsule at the start, middle and end)



Adapted from M.Phillips and C.Tibbs, A guide to managing diarrohoea in patients with PEI. Mylan Feb 16.