

GUIDELINES FOR PRESCRIBING PANCREATIC ENZYME REPLACEMENT THERAPY (PERT)

This guideline is designed for use in the following patient groups:

- *Pancreatic cancer (adenocarcinoma and variants)*
- *Post-pancreaticoduodenectomy (Whipple's)*
- *Post-extended distal pancreatectomy*
- *Ampullary cancer and distal cholangiocarcinoma*

Diagnosis of Pancreatic Exocrine Insufficiency

Pancreatic Exocrine Insufficiency (PEI) is very common in pancreatic cancer and causes impaired digestion, which commonly manifests in the symptoms described below (1). Reduced digestion results in maldigestion and this can lead to malnutrition and further weight loss (1, 2). It can also negatively impact on quality of life (3, 4). Treatment of PEI has been shown to improve survival in patients who have resectable or unresectable pancreatic cancer (5, 6, 7).

Assessment for the presence of the following symptoms is required to make a diagnosis of PEI, and should be subsequently utilised to instigate or increase PERT:

- Pale/offensive smelling stools (may leave an oily appearance around the toilet bowl)
- Stools that are difficult to flush/containing undigested food
- Increased stool frequency/volume/urgency
- Loose stools/diarrhoea, especially after food
- Abdominal discomfort/bloating, especially after food
- Indigestion/flatulence (malodorous)
- Hypoglycaemia in patients with diabetes mellitus
- Fat-soluble vitamin deficiencies
- Weight loss, although other factors such as anorexia, cachexia and pain may contribute to this, independent of PEI

Risk factors for PEI (1, 8)

- Pancreatic cancer, especially if the tumour is located in the head or neck
- Pancreatic duct dilatation towards the pancreatic head region
- Ampullary cancer, distal cholangiocarcinoma and Intraductal Papillary Mucosal Neoplasms (IPMNs) can also cause pancreatic duct dilation
- Surgery: Pancreaticoduodenectomy (Whipple's), extended distal pancreatectomy, gastrojejunostomy (including palliative bypass or gastrectomy)
- Other medical conditions including, but not exclusive to: type 1 and 2 diabetes, chronic pancreatitis, inflammatory bowel disease and coeliac disease

However, it is important to highlight that there are different causes of malabsorption in pancreatic cancer and following pancreatic resection, which predispose to similar symptoms, as described above. Anxiety, infection, biliary obstruction, medications, e.g. metformin; bile salt malabsorption, bacterial overgrowth and chemotherapy may also cause unwanted gastrointestinal symptoms and should be considered as differential diagnoses.

Testing for PEI

There is currently no consensus on the most appropriate test for PEI. Routine testing for PEI should not be undertaken unless there is doubt in the diagnosis, e.g. the patient's symptoms are not responding to PERT. In this situation, consider use of faecal elastase testing (FE-1) (9)*. Undertaking FE-1 may be considered at baseline if symptoms are not fully typical of PEI or in patients at lower risk of PEI (e.g. distal pancreas/IPMN).

**faecal elastase measures endogenous human elastase-1 and is therefore a marker of pancreatic enzyme secretion and not PEI. It does not detect exogenous porcine enzymes, so the test is viable whilst the patient is taking PERT. Interpretation of any result should be alongside symptom evaluation, as exact cut-off levels in each clinical scenario cannot be established. Please note that the FE-1 level will not increase following administration of PERT for the reasons detailed above, so repeat FE-1 testing is usually not indicated. Testing of FE-1 is also not accurate in watery stools.*

Patients with a tail of pancreas cancer or those who have had a classic distal pancreatectomy have a lower risk of PEI. There is usually sufficient pancreatic parenchyma remaining to secrete pancreatic enzymes allowing for normal digestion. However, symptoms should always be reviewed, as above, and PERT instigated for a trial period if there is any doubt regarding the presence of PEI.

Patients may present for assessment already receiving PERT, either Creon or Nutrizym. It is important to highlight to the patient that PERT is porcine-based and there is no alternative in the UK. Further information is available to patients where there may be potential religious implications of taking PERT (see A Guide to Taking Pancreatic Enzymes (Creon) (432)). It is imperative that the clinician reviews the patient's gastrointestinal symptoms at each consultation, adjusting the dose of PERT, if appropriate, or identifying other possible causes for their symptoms.

Pancreatic juice contains digestive enzymes, including lipase, amylase and protease, which help digest the fat, carbohydrate and protein in food, respectively. Amylase and protease are also produced in saliva and by the stomach, respectively. Any reference or rationale to justify PERT dosing and prescription is predominantly based on the units of lipase required, which are not produced exogenous to the pancreas. The following PERT preparations are available:

- *Creon 25000 units (Mylan: 25000 units lipase per capsule)*
- *Nutrizym 22 (Merck: 22000 units lipase per capsule)*
- *Pancrex V powder (Essential Pharmaceuticals Ltd: 25000 units lipase per gram) [2.5ml medical teaspoon = 2g Pancrex V powder]*

Rationale for starting dose

Pancreatic enzyme replacement therapy has been shown to improve weight gain in patients with advanced pancreatic cancer by improving digestion and nutrient absorption (10). In this study by Bruno et al, patients were commenced on 50000 units of lipase with meals and 25000 units with snacks as a starting dose. The pancreas typically produces 720000 units of lipase for an average 300-600 calorie meal. Around 10% of this value is required to maintain normal net digestion.

At diagnosis, patients often have advanced pancreatic cancer. Therefore, an increase in pancreatic duct dilatation due to disease progression is possible. Pancreatic enzyme secretion may also reduce over time due to advancing disease or post-pancreatic resection, so the requirement for PERT may increase with time. Patients are also typically

asked to fortify their diet to promote weight stability; this may often involve consuming more than 300-600 calories in a meal/snack. Education should be provided to empower patients to make the link between PERT use and normalisation of digestion.

Recommended starting doses of PERT and titration schedules are shown in **Figure 1** with PERT dose conversions shown in **Table 1**. It is also important to explain to the patient the reason that they need to take PERT, along with providing dietary advice and supporting literature.

PEI - other considerations

- *All patients taking PERT should be prescribed a low dose proton pump inhibitor (PPI), e.g. Omeprazole 20mg bd or equivalent, morning and evening (30 minutes before eating for effect). This may improve the efficacy of PERT. Additionally, a PPI may preserve pancreatic tissue/volume in post-surgical patients (12).*
- *Steatorrhoea may be masked by analgesia, especially opiates. Constipation can occur along with malabsorption, and this shouldn't be seen as a reason not to increase PERT, if appropriate.*
- *Patients should not reduce their fat intake to manage symptoms or reduce PERT dosing without support from a member of the team. Restricting fat intake may cause unintentional weight loss.*
- *If patients have jaundice, symptoms may be due to biliary malabsorption. Therefore, wait until jaundice has resolved before increasing PERT dose as per algorithm*
- *Commencing PERT facilitates adequate carbohydrate digestion, therefore blood glucose levels may increase and should be monitored*

Other causes of symptoms if no resolution with high-dose PERT (13)

Recommendation is for ongoing symptoms to be assessed by a Hepato-pancreatico-biliary (HPB) specialist dietitian with an expertise in PEI and a **referral to gastroenterology** is highly recommended.

Small bowel bacterial overgrowth (SIBO), an accumulation of bacterial in the small intestine, can commonly occur after chemotherapy and gastrointestinal (GI) surgery. There is no gold-standard test for diagnosing SIBO and 10-15% patients with negative results will have SIBO. Antibiotic treatment suggested as per **Figure 2**.

Bile acid malabsorption (BAM) occurs if there is a defect affecting the ability to absorb bile acids in the terminal ileum. Common causes include; GI surgery, chemotherapy and pancreatic disease. Diagnosis of BAM can be made using 23-seleno-25-homotaurocholic acid (SeHCAT) scan, C4 blood test or trialling a bile acid sequestrant.

- Treatment options include:
 1. Restricting dietary fat
 - Under the care of a specialist dietitian; reduce dietary fat into to 20% of total calories
 2. Antidiarrhoeal medication
 3. Bile acid sequestrant

'Mild' BAM may be treated using options 1 and 2. Usually, option 3 (bile acid sequestrants) are required for 'moderate' and 'severe' BAM. In addition, most patients with severe BAM need advice about long-term dietary fat reduction. Patients with steatorrhoea usually require colestevlam. Patients with moderate/severe BAM may be deficient in trace

elements and fat-soluble vitamins. These should be checked periodically and supplemented as appropriate.

Summary of recommendations

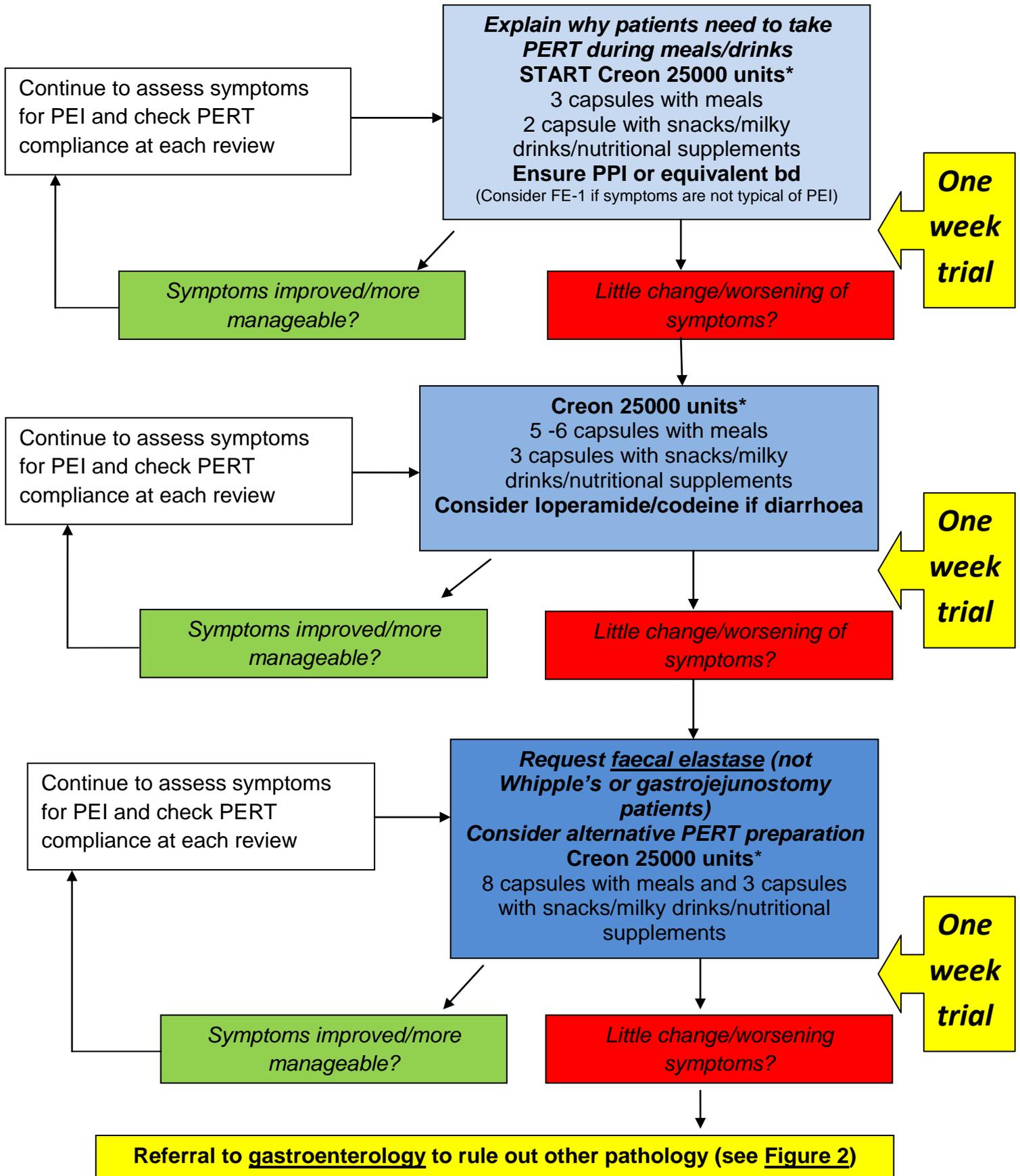
- **ALL** patients with head/neck of pancreas cancer or who have had a pancreaticoduodenectomy are very likely to require PERT and should be carefully assessed.
- Patients with a body/tail of pancreas cancer, or who have had a distal pancreatectomy should be assessed for symptoms of PEI and prescribed PERT only if appropriate.
- Patients with ampullary cancer, distal cholangiocarcinoma and IPMNs should also be assessed for symptoms of PEI and prescribed PERT only if appropriate.
- Treatment with PERT should be individualised based on symptom evaluation and nutritional status of the patient at each consultation. It should be prescribed to be taken with meals and snacks +/- nutritional supplements, as required.
- Provide education to patients regarding the correct administration of PERT (at the start and throughout the meal/snack/nutritional supplement). Liaison with Dietitian or clinical nurse specialist (CNS) should be considered.
- Consider PPI prescription, as detailed above, when prescribing/adjusting PERT.
- Routine FE-1 testing is not necessary in all patients. However, if symptoms do not respond to an increase in PERT, it should be considered along with referral to a local Gastroenterology unit to rule out other pathology. If FE-1 is normal, reassess symptoms and review potential differential diagnosis; if symptoms are in keeping with PEI, continue PERT

References

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Figure 1: As a guide, PERT should be started/adjusted as below:



**If a patient is prescribed Nutrizym 22 at initial assessment and would prefer to continue with this medication, titrate up the dose accordingly to above recommendations as required.*

Figure 2: If symptoms persist despite high dose of PERT, referral to gastroenterology is recommended to rule out other pathology:

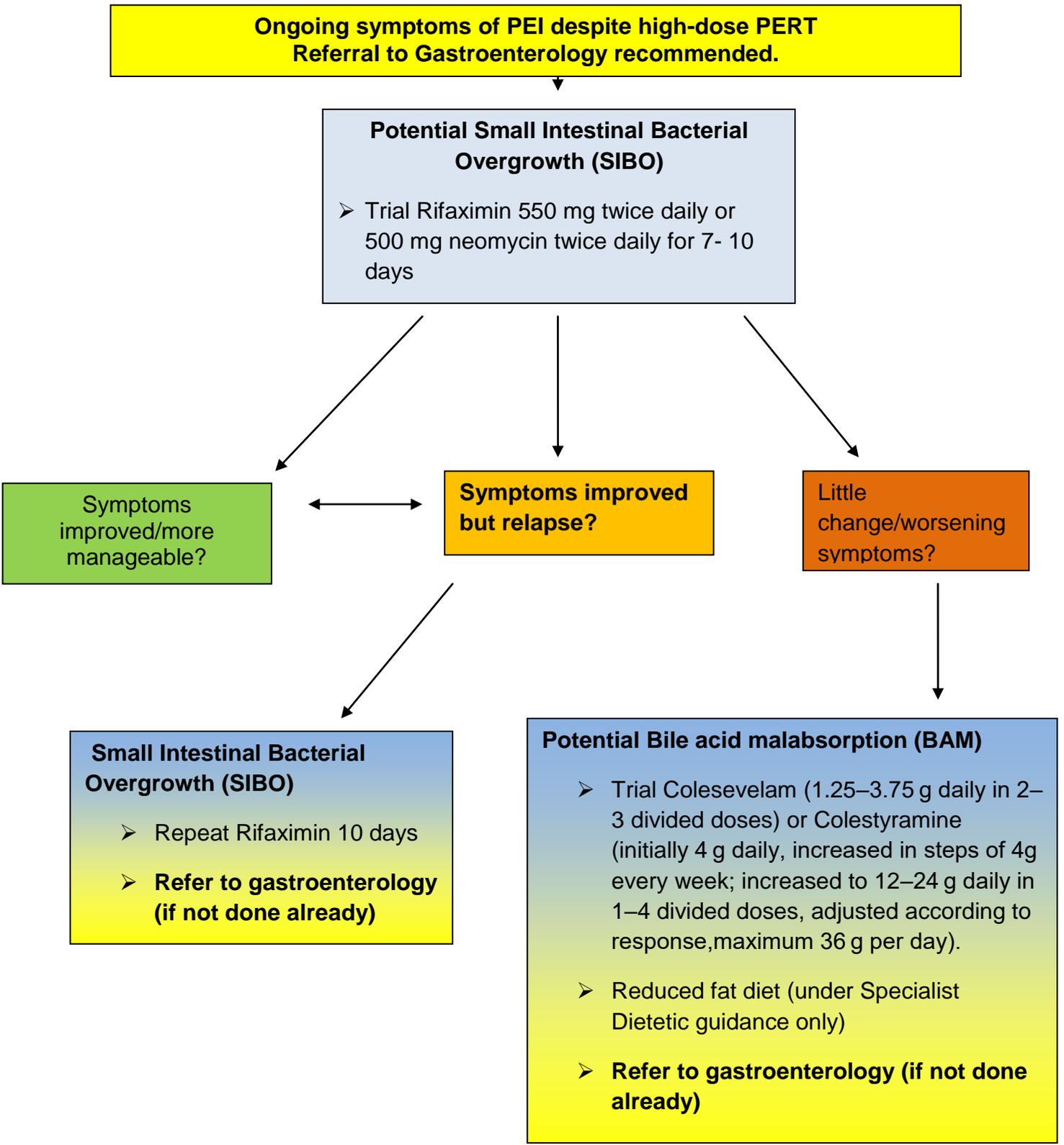


Table 1: PERT dose conversion

Prescribed dose of lipase units	Number of Creon 25000 unit capsules	Number of Nutrizym 22 capsules
<i>50000</i>	2	2
<i>75000</i>	3	4
<i>100000</i>	4	4-5
<i>125000</i>	5	5-6
<i>150000</i>	6	7
<i>175000</i>	7	8
<i>200000</i>	8	9

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