Diagnosis and management of pancreatic exocrine insufficiency

Mehrdad Nikfarjam1,2, Jeremy S Wilson3, Ross C Smith4, Australasian Pancreatic Club Pancreatic Enzyme Replacement Therapy Guidelines Working Group

Pancreatic exocrine insufficiency (PEI) occurs when normal digestion cannot be maintained due to insufficient pancreatic digestive enzyme activity in the small intestines.1 PEI has non-specific symptoms shared with other pancreatic diseases and gastrointestinal conditions2–3 and can result from damage to the pancreas where gross alteration of structure or functional change occurs.1

The main clinical PEI symptoms are steatorrhoea or diarrhoea, abdominal pain and weight loss.3 If left untreated, PEI can lead to malnutrition and related complications,6 as well as poor quality of life due to persistent gastrointestinal symptoms.4,9 An early and accurate PEI diagnosis and successful treatment are clinically important and of clear benefit to patients.3

Methods

This article summarises the Australasian guidelines for the management of pancreatic exocrine insufficiency, published by the Australasian Pancreatic Club (APC) in 2015.9 The guidelines apply a diagnostic algorithm to categorise patients into three groups based on the likelihood of PEI: definite, possible, and unlikely.9 The recommendations are based on the Oxford Centre for Evidence-based Medicine system for grading the level of evidence (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009), with the addition of level 3c: critical review of literature (Box 1). Strength of agreement for recommendations was gauged through electronic questionnaires distributed to the members of the working group.

Recommendations

Prevalence

A number of diseases and conditions are known to be associated with PEI. For example, PEI is estimated to occur in 94% of patients with chronic pancreatitis (10–15 years after clinical onset),10,11 >85% of patients with cystic fibrosis;12–14 74% of patients after pancreatic resection surgery;15 and 92% of patients with unresectable pancreatic cancer.15 The general level of PEI prevalence (high to low probability) can be assigned to different patient populations (Box 2).9

There are limited reliable data on the prevalence of PEI in the general population.9 PEI often goes undetected and patients referred from primary care may not represent the majority of PEI sufferers within the community.3,4,17,18

Pathophysiology

Various factors, including extrapancreatic conditions, may reduce pancreatic enzyme activity within the intestinal lumen if they interrupt the chain of events required for normal meal digestion. Failure at any stage in the process — which includes pancreatic stimulation, synthesis and release of digestive enzymes by pancreatic acinar cells, enzyme transportation through the duct system, and synchronised mixing of the pancreatic secretions with ingested food — may lead to PEI.9

The pathophysiology of PEI has four possible aetiologies:1

- Damage: the pancreatic parenchyma is no longer able to synthesise the required amounts of digestive enzymes.
- Asynchrony: dissociation of normal postprandial digestive enzyme secretions and intestinal meal delivery. This can occur in conditions such as short bowel syndrome, Crohn’s disease or after gastric, biliary or pancreatic resections or bypass procedures.

Guideline summary

Abstract

Introduction: In 2015, the Australasian Pancreatic Club (APC) published the Australasian guidelines for the management of pancreatic exocrine insufficiency (http://pancreas.org.au/2016/01/pancreatic-exocrine-insufficiency-guidelines). Pancreatic exocrine insufficiency (PEI) occurs when normal digestion cannot be sustained due to insufficient pancreatic digestive enzyme activity. This may be related to a breakdown, at any point, in the pancreatic digestive chain: pancreatic stimulation; synthesis, release or transportation of pancreatic enzymes; or synchronisation of secretions to mix with ingested food.

Main recommendations: The guidelines provide advice on diagnosis and management of PEI, noting the following:

- A high prevalence of PEI is seen in certain diseases and conditions, such as cystic fibrosis, acute and chronic pancreatitis, pancreatic cancer and pancreatic surgery.
- The main symptoms of PEI are steatorrhoea or diarrhoea, abdominal pain, bloating and weight loss. These symptoms are non-specific and often go undetected and untreated.
- PEI diagnosis is predominantly based on clinical findings and the presence of underlying disease. The likelihood of PEI in suspected patients has been categorised into three groups: definite, possible and unlikely.
- If left untreated, PEI may lead to complications related to fat malabsorption and malnutrition, and have an impact on quality of life.
- Pancreatic enzyme replacement therapy (PERT) remains the mainstay of PEI treatment with the recommended adult initial enzyme dose being 25 000–40 000 units of lipase per meal, titrating up to a maximum of 75 000–80 000 units of lipase per meal.
- Adjunct acid-suppressing therapy may be useful when patients still experience symptoms of PEI on high dose PERT.
- Nutritional management by an experienced dietitian is essential.

Changes in management as a result of these guidelines: These are the first guidelines to classify PEI as being definite, possible or unlikely, and provide a diagnostic algorithm to facilitate the early diagnosis of PEI and appropriate use of PERT.

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Decreased endogenous stimulation: decreased stimulation of \(C15\) obstruction: pancreatic duct blockage affects the transport of digestive enzymes and other secretions into the duodenum.

Decreased endogenous stimulation: decreased stimulation of enzyme production is particularly noted with coeliac disease.

Pancreatic exocrine secretions may be substantially reduced without producing clinical manifestations of PEI. Pancreatic lipases, for example, need to be reduced to 5% and the high reserve capacity of the pancreas. The mechanisms for the development of PEI and its clinical consequences are summarised in Box 3.

**Guideline summary**

1 Levels of evidence*

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Systematic reviews (with homogeneity) of RCTs</td>
</tr>
<tr>
<td>1b</td>
<td>Individual RCTs (with narrow confidence interval)</td>
</tr>
<tr>
<td>1c</td>
<td>All or none RCTs</td>
</tr>
<tr>
<td>2a</td>
<td>Systematic reviews (with homogeneity) of cohort studies</td>
</tr>
<tr>
<td>2b</td>
<td>Individual cohort study or low quality RCTs (eg, &lt; 80% follow-up)</td>
</tr>
<tr>
<td>2c</td>
<td>Outcomes research; ecological studies</td>
</tr>
<tr>
<td>3a</td>
<td>Systematic review (with homogeneity) of case–control studies</td>
</tr>
<tr>
<td>3b</td>
<td>Individual case–control study</td>
</tr>
<tr>
<td>3c</td>
<td>Critical review of the literature, including multiple experimental and observational studies</td>
</tr>
<tr>
<td>4</td>
<td>Case series (and poor quality cohort and case–control studies)</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles</td>
</tr>
</tbody>
</table>


- Obstruction: pancreatic duct blockage affects the transport of digestive enzymes and other secretions into the duodenum.
- Decreased endogenous stimulation: decreased stimulation of enzyme production is particularly noted with coeliac disease.

Pancreatic exocrine secretions may be substantially reduced without producing clinical manifestations of PEI. Pancreatic lipases, for example, need to be reduced to 5–10% of normal post-prandial levels before steatorrhoea, the main PEI clinical symptom, is evident. This is linked to compensatory enzyme mechanisms and the high reserve capacity of the pancreas. The mechanisms for the development of PEI and its clinical consequences are summarised in Box 3.

**Diagnosis**

The symptoms of PEI are gastrointestinal-related and non-specific. If undiagnosed, patients may have ongoing symptoms such as diarrhea and abdominal pain that can sometimes be mistaken as a functional bowel disorder. PEI symptoms can vary from patient to patient, and are dependent on the degree of PEI experienced and its aetiology.

In practice, an initial suspicion of PEI is based on the clinical assessment of the patient, self-reported bowel movements, and weight loss (or failure to thrive in children). However, an important factor to remember is that the reliance on patient symptoms alone may lead to under- or over-diagnosis.

Morphological and functional assessments can be made to confirm diagnosis (Box 4). Initially, computed tomography can identify gross pancreatic structural changes and is readily available. However, these changes are not always specific and may require further investigation with magnetic resonance imaging, endoscopic ultrasound and, rarely, secretin-enhanced magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography. Additionally, PEI may still occur in patients with a morphologically normal pancreas. Direct functional tests, such as the secretin–cholecystokinin stimulation test and endoscopic pancreatic function test, involve the collection of pancreatic secretions while the pancreas is stimulated. Direct tests are sensitive and specific, but are also invasive, costly and therefore have limited routine clinical use. Indirect functional tests (eg, faecal, breath and blood tests) are cheaper and easier to use, but are generally less sensitive and less specific. Screening for nutritional markers in the blood, including magnesium, fat-soluble vitamins and lipoproteins, can help assess nutritional deficiencies and may be used to support a PEI diagnosis as well as to monitor treatment effectiveness.

**Likelihood of pancreatic exocrine insufficiency (PEI) in various patient populations**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Likelihood of PEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis (pancreatic insufficiency)</td>
<td>100% (definite)</td>
</tr>
<tr>
<td>Total pancreatectomy</td>
<td></td>
</tr>
<tr>
<td>Severe chronic pancreatitis (with calcific changes, steatorrhoea, weight loss)</td>
<td></td>
</tr>
<tr>
<td>Tumour destroying head of pancreas</td>
<td></td>
</tr>
<tr>
<td>Acute pancreatitis destroying head of pancreas</td>
<td></td>
</tr>
<tr>
<td>Mild and moderate chronic pancreatitis</td>
<td>30–70% (possible)</td>
</tr>
<tr>
<td>After severe acute pancreatitis</td>
<td></td>
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<tr>
<td>After severe pancreatitis</td>
<td></td>
</tr>
<tr>
<td>After pancreatic surgery (Whipple procedure)</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>&lt; 10% (unlikely)</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td></td>
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<tr>
<td>Coeliac disease</td>
<td></td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td></td>
</tr>
<tr>
<td>Older people (with weight loss)</td>
<td></td>
</tr>
<tr>
<td>Bowel resection</td>
<td></td>
</tr>
</tbody>
</table>

* Adapted from the Australasian Pancreatic Club guidelines.  † Diseases and conditions either associated with or known to cause PEI. ‡ After pancreatic surgery in the setting of pancreatic cancer (which is often associated with chronic pancreatitis) and in the setting of chronic pancreatitis alone may be more definite indications for PEI.  

**Mechanisms for the development of pancreatic exocrine insufficiency and its clinical consequences**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis, acute pancreatitis, chronic pancreatitis, bowel surgery, pancreatic surgery, gastric surgery, coeliac disease, ageing pancreas</td>
<td>Abdominal pain, flatulence, diarrhoea, steatorrhoea (fothy, foul-smelling, buoyant stools), weight loss (failure to thrive in children)</td>
</tr>
<tr>
<td>Loss of working pancreatic parenchyma</td>
<td>Postprandial asynchrony</td>
</tr>
<tr>
<td>Reduced stimulation of enzyme production</td>
<td>Ductal obstruction</td>
</tr>
<tr>
<td>Duodenal lipase levels fall below 5–10% of normal postprandial levels</td>
<td></td>
</tr>
<tr>
<td>Pancreatic exocrine insufficiency, malabsorption</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>Low levels of:</td>
<td></td>
</tr>
<tr>
<td>Micronutrients</td>
<td>Fat-soluble vitamins (A, E, D, K)</td>
</tr>
<tr>
<td>Lipoproteins</td>
<td></td>
</tr>
<tr>
<td>Reduced quality of life</td>
<td>Increased morbidity and malnutrition-related complications (eg, osteopenia and bone fracture)</td>
</tr>
</tbody>
</table>

* Adapted from the Australasian Pancreatic Club guidelines.
The 2015 PEI management guidelines\(^9\) graded patients with clinically suspected PEI into three subgroups with corresponding recommended investigations and treatment options (Box 4):

- **PEI definite**: if the presentation falls within this group, a diagnosis of PEI can be made solely on clinical grounds. In this situation, gross changes to the pancreas are present (eg, total pancreatectomy or radiologic investigations show severe calcific pancreatitis or neoplasms in the head of the pancreas) along with symptoms suggestive of severe steatorrhea, weight loss and fat-soluble vitamin deficiency.

- **PEI possible**: if only moderate pancreatic structural changes are seen, then a PEI diagnosis is suggested if the patient also presents with nutritional impairment and diarrhoea, although there could be other reasons for these symptoms. The probability of a positive objective test, and therefore response to pancreatic enzyme replacement therapy (PERT), is 30–70%.

- **PEI unlikely**: conditions seen within this group may only occasionally be associated with or caused by PEI. PEI symptoms are likely to be seen in < 10% of cases and the probability of a positive objective test and response to PERT is estimated to be < 10%.

Although these guideline recommendations were produced through a consensus process in light of the best available evidence, they are not yet validated.

### Complications

If left untreated, PEI can lead to serious complications including:

- Weight loss and malnutrition\(^{6,11,26}\)
- Nutritional deficiencies: malabsorption of micronutrients (including zinc, magnesium, calcium, thiamine and folic acid) and lipid-soluble vitamins increases the risk of malnutrition-related complications.\(^6\) Almost two-thirds of patients with chronic pancreatitis have either osteoporosis or osteopenia (combined prevalence rate of 65%).\(^{27}\) PEI in these patients is significantly correlated with reduced bone mineral density and decreased levels of the fat-soluble vitamin D required for normal bone metabolism.\(^{27,28}\)
- Reduced quality of life\(^{8,29,30}\) related to persistent gastrointestinal and pain symptoms, as well as other factors such as inability to work and financial strain.\(^8\)
- High morbidity and mortality through the increased risk of malnutrition-related complications and cardiovascular events.\(^{31-33}\)

### Management

The primary treatment goal for PEI is to restore the normal digestion process in order to maintain adequate nutrition. PEI-related symptoms also need to be alleviated and disease progression prevented. The fundamental elements of current PEI management in adults are outlined in the PEI management algorithm in Box 5.\(^5,9,34\)

- **PERT** (evidence level 1b);
- lifestyle modifications: primarily alcohol abstinence, cessation of smoking and consumption of a well balanced diet (level 5);
- trial of acid-suppressing agents in patients who continue to experience symptoms of PEI despite high doses of PERT (level 1b);
- diet adjustments: small frequent meals, normal fat intake and vitamin supplementation (lipid-soluble vitamins A, D, E and K) (level 5); and
- follow-up of patients: focusing on nutritional deficiencies, symptoms of maldigestion, treatment of any causative diseases and ensuring treatment compliance (level 5).

## Pancreatic enzyme replacement therapy

PERT is the mainstay of PEI treatment. Encapsulated microgranules deliver pancreatic extracts (a combination of lipase, amylase and protease) into the duodenal lumen, providing sufficient enzymatic activity so that nutrient digestion is restored and malabsorption is prevented.\(^{23}\)

The microgranules are taken with a meal and mix intragastrically with the chyme, but are protected from acid degradation by an enteric coating. They are then released from the stomach along with the chyme into the duodenum. The pH-sensitive coating dissolves in the duodenum’s alkaline environment, releasing the enzymes at the optimum point for digestion and absorption. Variation in enzyme content, the size of the enzyme particles and the dissolution properties of the enteric coating can influence the effectiveness of PERT and the bioequivalence of different formulations.\(^1\)

Some patients may require adjuvant treatment with acid suppressors (eg, proton pump inhibitors) if the pH of their duodenum is lower than normal (eg, in patients with bicarbonate deficiency; level 1b). A lower pH may affect the dissolution of the enteric coating and reduce the effectiveness of enzymes.\(^1\)

PEI severity varies from patient to patient, and the relationship between the dose of pancreatic enzymes and response to therapy is

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**Clinical presentation**

**Signs and symptoms**: Steatorrhea/diarrhoea, abdominal pain, flatulence, weight loss (adults)/failure to thrive (children), micronutrient deficiency, low fat-soluble vitamers and lipoproteins

**Comorbidity**: Osteoporosis

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**4 Pancreatic exocrine insufficiency (PEI): diagnostic pathway**

![PEI Pathway Diagram](image-url)

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Guideline summary

5 Pancreatic exocrine insufficiency (PEI) management (adults)

- Refer patient to dietitian for nutritional assessment, counselling and support
- Initiate PERT 25 000–40 000 units lipase with each meal
- Assess at baseline and the response to PERT at least annually
- GI symptoms
- Nutritional parameters
  - body weight
  - anthropometric parameters
  - vitamins A, D, E, K, B12, iron, calcium and zinc levels
- Increase dosage to maximum 75 000–80 000 units lipase each meal or maximum 10 000 units lipase/kg bodyweight/day
- Insufficient response
- Trial acid-suppressing agents

* Adapted from the Australasian Pancreatic Club guidelines.

Changes in management

PEI is an underdiagnosed and often undertreated condition. The dilemma for the clinician, therefore, is to be able to determine which patients will benefit from further investigations and PEI treatment. The latest guidelines for the management of PEI, developed by the APC, grade presentation types and likelihood of PEI being present (ie, definitely, possibly and unlikely PEI). In this way, the difficulties of diagnosing PEI can be taken into account, while relating the value of investigation and treatment to each diagnostic category. The guidelines also provide consensus recommendations on the use of PERT for each category.


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References:


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