Pancreatic Exocrine Insufficiency
Diagnosis and Treatment in Chronic Pancreatitis and Pancreatic Cancer

Release Date: May 1, 2011
Expiration Date: May 1, 2012

Statement of Need
Pancreatic exocrine insufficiency (PEI) is a serious condition with multiple causes, including chronic pancreatitis (CP), pancreatic cancer (PC), cystic fibrosis, and gastrointestinal surgeries, among others. Although progress has been made in the understanding of the epidemiology and pathophysiology of CP and PC as relevant to the etiology of PEI, this information has not been disseminated widely; early diagnostic testing for CP, including pancreatic function testing, is underused; and early detection of PC often is not achieved. In addition, evidence-based recommendations for the treatment of CP are lacking, and recommendations for the treatment of PEI in PC lack detail. Finally, approved treatments for PEI have become available only recently, and only one of these has specific dosing guidelines for PEI in CP and pancreatic cancer. Clinician education is needed to close these gaps.

Goal
The goal of this activity is to educate oncologists, gastroenterologists, and other health care professionals in the latest evidence regarding the diagnosis and management of PEI.

Learning Objectives
At the completion of this activity, participants should be better prepared to:

- Delineate the epidemiology and pathophysiology of CP and PC, including how these conditions can lead to PEI and the significance of PEI for nutritional health.
- Use current techniques to assess and diagnose CP and PC, with attention to the presence of PEI.
- Evaluate therapies for PEI in CP and PC, including the role of pancreatic enzyme supplementation (PES) in improving nutritional health.
- Identify appropriate dosing of PES for PEI in CP, PC, and pancreatectomy.

Intended Audience
Oncologists, gastroenterologists, and other health care professionals with an interest in the treatment of PEI.

Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCCME) through the joint sponsorship of Columbia University College of Physicians and Surgeons and Applied Clinical Education (ACE). Columbia University College of Physicians and Surgeons is accredited by the ACCME to provide continuing medical education for physicians.

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Financial Disclosures
Peter D. Stevens, MD: Boston Scientific (consultant).
Jerome H. Siegel, MD, RPh, MACG, FASGE, AGAF: nothing to disclose.
Oren Traub, MD, PhD: nothing to disclose.

Disclosure of Unlabeled Use
This educational activity may contain discussion of some agents that have been studied but are not FDA-approved for use in the treatment of PEI. Please refer to official prescribing information for all products for discussion of approved indications, contraindications, and warnings.

Method of Participation
There are no fees for participating in and receiving credit for this activity. The participant should, in order, read the objectives, disclosures, and monograph; take the post-test; and complete the online activity evaluation at www.CMEZone.com. Enter project number MN112 in the keyword field to access this activity.

Financial Support
No hard copy or faxed submissions will be accepted. A score of at least 70% is required to complete this program successfully. One retake is allowed. The corrected answer sheet will be provided for comparison with course information.

Conflict of Interest Statement
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Introduction

Pancreatic exocrine insufficiency (PEI) can result from a variety of underlying disorders, including chronic pancreatitis (CP) and pancreatic cancer (PC), and has serious implications for both intermediate and long-term health. Diagnosis of PEI arising from pancreatic conditions can be complex, and regulatory changes related to pancreatic enzyme supplementation (PES) during the past decade have affected treatment options. This monograph provides an overview of the epidemiology, pathophysiology, and diagnosis of CP, PC, and PEI and reviews current management of PEI arising in the context of pancreatic disorders.

Epidemiology and Pathophysiology

Chronic Pancreatitis

Chronic pancreatitis is a syndrome involving progressive inflammatory changes in the pancreas that result in permanent structural damage, leading to impairment of exocrine and endocrine function. The pathogenesis of CP appears to be multifactorial, although several distinct events have been identified. The first is a decrease in bicarbonate secretion, due to either functional impairment caused by genetic abnormalities of the ductal cells or mechanical obstruction such as strictures or tumors, leading to ductal plugs or stone formation. The second involves intraparenchymal activation of digestive enzymes within the pancreatic gland. This may be due to genetic abnormalities that cause direct impairment in enzyme activation and regulation or predispose to toxic injury from environmental exposures, such as alcohol.

The prevalence of CP is estimated at 0.04% to 5%, with the variation in figures attributed to the fact that some cases of CP are clinically silent. Chronic excessive alcohol use accounts for the majority of cases—roughly two-thirds—of CP in the Western world. However, less than 10% of alcoholics develop CP, which suggests that other factors, including genetic susceptibility or underlying anatomic abnormality, may be necessary for alcohol-induced pancreatitis to occur.

Primary genetic traits are important, albeit less frequent, causes of CP. The main genetic cause of CP is hereditary pancreatitis, which is transmitted as an autosomal dominant trait with incomplete (80%) penetrance. The majority of affected individuals develop symptoms before the age of 20, and often before the age of 5. Hereditary pancreatitis also is associated with an increased risk for pancreatic adenocarcinoma.

Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that result in altered lung function in patients with cystic fibrosis (CF) also can affect pancreatic exocrine function. Indeed, most patients with CF develop progressive pancreatic damage as a result of defective ductular and acinar pancreatic secretions.

Other causes of CP include ductal obstruction (eg, trauma, pseudocysts, stones, tumors, possibly pancreas divisum), various systemic diseases (eg, systemic lupus erythematosus, hypertriglyceridermia, hyperparathyroidism), and autoimmune disease. Chronic pancreatitis of unknown etiology (idiopathic pancreatitis) comprises between 30% and 40% of cases, although some studies suggest that underlying mutations in the CFTR gene are responsible for at least a portion of these cases.

Pancreatic Cancer

The commonly used term, pancreatic cancer, refers to ductal pancreatic adenocarcinoma, which accounts for approximately 80% of patients with a pancreatic malignancy. Ductal adenocarcinoma has an incidence of approximately 10 per 100,000 individuals annually in the Western world. Another 10% of pancreatic tumors arise from exocrine tissue and include acinar cell carcinoma, cystadenocarcinoma, giant cell carcinoma, and intraductal papillary mucinous neoplasm. The remaining pancreatic malignancies are caused by neuroendocrine tumors, such as insulinoma, gastrinoma, and endocrine-inactive tumors. Neuroendocrine tumors are less common, with an incidence of approximately 2.5 per 100,000 individuals per year.

The pathophysiology of pancreatic tumors is similar to that of other malignancies in which inherited or acquired genetic mutations result in unregulated growth and dedifferentiation of normal pancreatic cells. Smoking is the most common known risk factor for pancreatic adenocarcinoma and is associated with an estimated 20% to 25% of all pancreatic tumors. Other risk factors associated with the development of pancreatic adenocarcinoma include heavy alcohol intake, Helicobacter pylori infection, obesity, diabetes mellitus, occupational exposures, non-O blood group, family history of PC, and hereditary pancreatitis. Although three-fourths of pancreatic neuroendocrine tumors are sporadic, one-fourth occur in the setting of multiple endocrine neoplasia.

Pancreatic Exocrine Insufficiency

During active secretion, pancreatic juice contains a mixture of zymogens (digestive enzymes in the preactivated form) that are produced by acinar cells, which then mix with a bicarbonate-rich fluid. In fact, the pancreas synthesizes more than a dozen different digestive enzymes, with the majority of enzyme activity deriving from trypsin, chymotrypsin, amylase, and lipase.

PEI describes the failure of the pancreas to deliver sufficient amounts of functional pancreatic enzymes to the intestine to digest the complex nutrients that are present in a meal. This can result from a variety of pathophysiologic changes on the protein levels (eg, enzyme degradation secondary to proteolytic degradation or low local pH), on the organ level (eg, alteration in the structure and function of the pancreas in response to various disease states or environmental exposures, ductal blockage or scarring, or surgical resection of the pancreas), or in other organ systems (eg, decreased central nervous system input to the pancreas, bowel disorder–induced mismatch in intestinal delivery of food relative to pancreatic exocrine capacity due to bowel disorders). Lipase function is particularly vulnerable to many of these factors, and thus, clinical evidence of lipase deficiency almost always precedes signs of deficiencies in other enzymes.

Causes of PEI include CP (including all the causes of CP described earlier), PC with or without pancreatectomy, celiac disease, Shwachman-Diamond syndrome (isolated pancreatic acinar cell dysfunction), and altered gastrointestinal motility in the setting of gastric resection, gastric bypass surgery, short bowel syndrome, Crohn’s disease, and diabetes mellitus (Figure 1). The reported incidence of PEI can vary widely among reports but is estimated at 10% to 40% of patients with CP, more than 50% of patients with PC, and more than 60% of patients undergoing pancreatic resection, with an even higher incidence depending on the degree of pancreatectomy.
Clinical Manifestations and Consequences

Chronic Pancreatitis

Although CP may be asymptomatic in some cases, the majority of patients experience abdominal pain and/or pancreatic insufficiency, which can consist of both PEI (see below) and pancreatic endocrine insufficiency (eg, diabetes mellitus).16

Abdominal pain is a dominant feature of CP and is responsible for most hospitalizations related to this illness. The pain typically is dull or boring in quality, is located in the epigastric area with radiation to the back, worsens after eating, occasionally is associated with nausea and vomiting, and may be relieved partially by sitting upright or leaning forward.1,16 One group of investigators detailed 2 types of pain patterns: type A, which was characterized by short, relapsing episodes lasting days to weeks, separated by pain-free intervals lasting from months to more than a year; and type B, which was prolonged, severe, and unrelenting, often requiring repeated hospitalizations.19 Some studies have demonstrated a gradual diminishment of pancreatic pain over years (ie, “pancreatic burnout”).16

Chronic pancreatitis also is associated with pseudocyst formation, bile duct or duodenal obstruction, pancreatic ascites or pleural effusion, splenic vein thrombosis, pseudoaneurysms,16 and PC, and is a known risk factor for PC (in fact, it may be difficult to distinguish between PC and CP). Patients may develop acute attacks of pancreatitis—particularly alcoholic who continue drinking.16 The condition is associated with considerable morbidity and mortality, frequent hospital admissions, and decreased quality of life.20 A Danish study reported a 4-fold higher mortality rate for those with CP relative to the general population.21

Pancreatic Cancer

Pain, weight loss, and jaundice are among the common signs and symptoms that prompt a diagnostic evaluation for PC. Pain is present in 80% to 85% of patients with locally advanced or advanced disease22,23 and usually is felt in the upper abdomen as a dull ache that radiates straight through to the back. It may be intermittent and made worse by eating.

Jaundice often is accompanied by pruritus and dark urine. In one series, painful jaundice was present in approximately half of patients with locally unresectable disease, whereas painless jaundice was present in approximately half of patients with a potentially resectable and curable lesion.22 Weight loss can be profound; it may be associated with anorexia, early satiety, or PEI (see below).23 The majority of patients with advanced cancer will develop PEI,17 and this figure is even higher in those who undergo surgical resection of pancreatic tissues.19 The initial presentation varies according to tumor location22,23, tumors in the pancreatic body or tail usually present with pain and weight loss, whereas those in the head of the gland typically present with malabsorption, weight loss, and jaundice.

Unfortunately, signs and symptoms of pancreatic adenocarcinoma do not usually manifest until the disease is advanced and unresectable. As a result, morbidity and mortality are high. According to the American Cancer Society, for all stages of PC combined, the 1-year survival rate is 20%, and the 5-year survival rate is 4%.24 Thus, despite being much less prevalent than other cancers, pancreatic adenocarcinoma is the fourth leading cause of cancer–related deaths in the United States and is second only to colorectal cancer as a cause of digestive cancer–related deaths.24 By contrast, neuroendocrine pancreatic cancer is more indolent and amenable to resection; hence, it is associated with better outcomes.25

Pancreatic Exocrine Insufficiency

Loss of lipolytic function typically is the first sign of PEI. It manifests with fat malabsorption and steatorrhea with loose, greasy, foul-smelling stools.13 Malabsorption of the fat-soluble vitamins (A, D, E, K) and vitamin B12 also may occur,26 leading to clinical evidence of vitamin deficiency in severe untreated PEI, including evidence of vitamin deficiency in severe untreated PEI, including...
metabolic bone disease and osteoporosis.27 Because of the presence of other compensatory digestive mechanisms (eg, salivary amylase, brush border proteases), protein and carbohydrate maldigestion may be rare and late occurrences in the course of the disease.28 Bacterial overgrowth is seen in more than one-third of patients with PEI and may contribute to diarrhea.29

Undiagnosed PEI can have a profound effect on overall wellness and quality of life. The classical clinical presentation of PEI is steatorrhea and weight loss in the adult and failure to maintain a normal rate of growth and development in the child or adolescent (failure to thrive).13 The deficiency in micronutrients, fat-soluble vitamins, and lipoproteins has been associated with higher morbidity secondary to the increased risk for malnutrition-related complications and cardiovascular events.13 Cardiovascular complications arise primarily from abnormalities in lipid metabolism and secondary atherosclerosis (Table 1).13,30,31

The exocrine capacity of the healthy pancreas greatly exceeds the enzymatic needs of normal food delivery to the intestines. Thus, clinical signs and symptoms of PEI may not occur until 90% of pancreatic function is lost.32 Thus, more subtle symptoms of intermittent bloating, abdominal pain, and diarrhea may be present prior to evidence of frank PEI.

Diagnoses in PEI

Chronic Pancreatitis

Diagnosis of CP is suspect in the presence of typical symptoms (eg, recurrent abdominal pain, malabsorption, diabetes mellitus), particularly in the presence of defined risk factors (eg, alcohol use, CF, recurrent acute pancreatitis, family history). It can, however, sometimes be difficult to establish definitively.16 Serum measurements of amylase or lipase and other routine blood tests typically are normal or nonspecific.16 An evaluation consistent with fat malabsorption due to PEI supports a diagnosis of CP.

Imaging studies showing calcifications, ductal dilatation, enlargement of the pancreas, and fluid collections (eg, pseudocysts) adjacent to the gland are indicative of CP.16 Calcifications can be seen on plain films, whereas the other described findings can be seen on computed tomographic (CT) scans or ultrasound and can corroborate a diagnosis of CP with reasonable sensitivity and specificity.16 Magnetic resonance cholangiopancreatography (MRCP) has emerged as a particularly useful imaging modality for the diagnosis of CP, as it is noninvasive and can demonstrate calcifications and pancreatic duct obstruction with good sensitivity and specificity.36,37,38

Endoscopic ultrasonography (EUS) is associated with less specificity than CT; however, it has greater sensitivity and is advantageous in allowing for the collection of tissue via EUS-guided fine-needle aspiration (FNA) of suspicious solid masses immediately during testing, rather than necessitating a second procedure. Features suggestive of CP on EUS include the presence of stones, visible side branches, cysts, lobularity, an irregular main pancreatic duct, hyperechoic foci and strands, dilation of the main pancreatic duct, and hyperechoic margins of the main pancreatic duct.16,34,35

Pancreatic Cancer

Several studies are available for the identification and staging of PC, including CT with a dedicated pancreas protocol (preferred),36 ultrasound or EUS, endoscopic retrograde cholangiopancreatography, magnetic resonance imaging, and MRCP.37,38 The diagnosis typically is made radiographically after a mass is detected within the pancreas, often obstructing the pancreatic duct or biliary tree.37,38 Unfortunately, early detection of PC is rare.37,38

The differential diagnosis of primary exocrine PC includes CP, pancreatic endocrine tumors, autoimmune pancreatitis, lymphoma, and a variety of other rare conditions. Histologic proof of malignancy is mandatory in unresectable cases or when preoperative treatment is planned.37,38 This can be accomplished percutaneously or via EUS with FNA.

Pancreatic Exocrine Insufficiency

A diagnosis of PEI is suspected in the context of typical symptoms (steatorrhea, malnutrition), particularly when an underlying disorder that causes PEI is present (eg, CP, PC, pancreatic resection, CF) (Table 2).39

First, a diagnosis of steatorrhea should be established definitely by 72-hour quantitative fecal fat testing; excretion of more than 7 g of fat per day is diagnostic of malabsorption, although patients with steatorrhea often have values greater than 10 g per day. In cases of non-steatorrheic malabsorption or diarrhea, appropriate testing should be performed to identify other causative disorders (eg, celiac disease, inflammatory bowel disease).

Second, pancreatic exocrine function should be assessed. Historically, this was accomplished via placement of a gastroduodenal (Dreiling) collection tube that aspired pancreatic secretions in response to an exogenous stimulus (eg, secretin, cholecystokinin, the Lundh test meal).39 Although this method previously resulted in poor accuracy, was invasive and inconvenient, and was poorly tolerated by patients,40 more advanced endoscopic techniques now enable use of this approach at some centers and result in high sensitivity for early PEI.

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Table 1. Consequences of Pancreatic Insufficiency13,30,31

<table>
<thead>
<tr>
<th>Fat Malabsorption</th>
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<tbody>
<tr>
<td>Steatorrhea</td>
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<tr>
<td>Vitamin deficiency</td>
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<tr>
<td>• Vitamin A (night blindness)</td>
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<tr>
<td>• Vitamin D (osteoporosis, metabolic bone disease)</td>
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<tr>
<td>• Vitamin E (neuropathy, anemia)</td>
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<td>• Vitamin K (coagulopathy)</td>
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<table>
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<tr>
<th>Dyslipidemia</th>
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<td>Adverse cardiovascular events</td>
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<table>
<thead>
<tr>
<th>Carbohydrate Malabsorption</th>
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<tr>
<td>Bloating</td>
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<table>
<thead>
<tr>
<th>Malnutrition</th>
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<tr>
<td>Hypoproteinemia</td>
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<tr>
<td>Edema</td>
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<tr>
<td>Weight loss</td>
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<tr>
<td>Growth retardation</td>
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</tbody>
</table>

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Regardless, indirect functional testing has supplanted direct testing for pancreatic endocrine function at most centers. Among various tests (stool chymotrypsin, breath tests, serum trypsinogen), measurement of fecal elastase-1 (a pancreatic enzyme) via enzyme-linked immunosorbent assay is the most sensitive and specific. In addition, its values are independent of pancreatic enzyme replacement therapy and require only a single random stool sample. A fecal elastase-1 value of less than 200 mcg/g indicates moderate to severe PEI (sensitivity and specificity >90%); the test may be less useful in detecting early or mild PEI.

Radiologic imaging typically is not useful in establishing a clinical diagnosis of PEI, but it can help determine the etiology of the condition. Structural changes evident on imaging can help support the diagnosis, and imaging studies are important to rule out pancreatic neoplasm. The utility of MRCP with secretin stimulation for the assessment of pancreatic exocrine function currently is under investigation. Different modes of breath testing also are being investigated for this purpose.

Another diagnostic modality for PEI is an empiric trial of anti-PEI therapy (enzyme supplementation). Response to such therapy is highly suggestive of PEI. This strategy could be considered in patients with established steatorrhea and a known causative pancreatic disorder (eg, CP, PC, pancreatic resection, CF) and may obviate the need for functional testing.

Once a diagnosis of PEI is established, additional testing should be considered to look for vitamin deficiencies and associated secondary complications (eg, metabolic bone disease, osteoporosis, impaired night vision, anemia, etc.).

Management of PEI

The goals of treatment for PEI are to relieve maldigestion-related symptoms (eg, bloating, diarrhea, steatorrhea) and restore nutritional health. Aside from potential treatments for the causative disorder, management of PEI is achieved via vitamin supplementation, oral pancreatic enzyme replacement therapy (PERT), and possibly dietary modification. The role of dietary modification in PEI is controversial. Some investigators and guidelines recommend limitation of fat content, whereas others suggest that the caloric delivery associated with fat intake is vital and that the inability to tolerate fat-containing meals should prompt adjustments in PERT therapy instead. Other proposed dietary modifications include frequent, low-volume meals that avoid difficult-to-digest foods, as well as the use of medium-chain triglycerides, which are absorbed directly by the intestinal mucosa and may be useful for providing extra calories in patients with weight loss as well as for reducing steatorrhea in those with a poor response to oral pancreatic enzymes. Vitamin supplementation can be achieved primarily through water-miscible forms (vitamins A, D, E, K, B12), although intramuscular injections of vitamin B12 occasionally are used. All patients with PEI should see a registered nutritionist for review of nutritional status and obtain detailed recommendations for dietary strategies, and individuals with PEI related to alcohol-induced CP should abstain from alcohol, a strategy that may restore a significant proportion of pancreatic exocrine function.

PERT is the mainstay of therapy for PEI. Clinical options for such therapy have changed dramatically in the past decade subsequent to an FDA requirement, in 2004, that manufacturers of all pancreatic enzyme preparations perform new randomized controlled trials (RCTs) and submit data via a New Drug Application in order to continue marketing their products. Prior to this ruling, PERT products varied greatly in terms of tolerability and therapeutic performance, mainly due to poor uniformity in enzyme content, stability, and inclusion of inert compounds. The proof-of-efficacy and safety requirements now include standardized enzyme delivery to the proximal small bowel, demonstrated improvement in fat absorption, and stability data to support the recommended shelf-life of the product. Since 2009, 3 porcine pancreatic enzyme products, formulated as delayed-release pancrelipase, have won the necessary approvals based on RCTs (Table 3, page 6).

Pancreatic enzyme supplements contain lipase, protease, and amylase, but therapy usually is guided by lipase replacement and improvement of steatorrhea. Enteric-coated preparations allow safe passage of pancreatic enzymes beyond the acidic environment of the stomach, whereas non–enteric-coated preparations may require the use of an acid-suppression agent (eg, H2-blocker, proton pump inhibitor) to prevent degradation of the enzymes. In most studies, enteric-coated formulations are superior to uncoated preparations in improving fat digestion, and formulations with smaller microspheres or mini-microspheres produced effects that were significantly superior to those of larger microsphere formulations.

### Table 2. Diagnostic Testing for Pancreatic Exocrine Insufficiency

<table>
<thead>
<tr>
<th>Test</th>
<th>Potential Drawbacks</th>
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<tbody>
<tr>
<td>Assessment for steatorrhea</td>
<td></td>
</tr>
<tr>
<td>Sudan staining</td>
<td>High variability results in poor sensitivity, reliability</td>
</tr>
<tr>
<td>24- and 72-h stool fat</td>
<td>Patient compliance sometimes difficult</td>
</tr>
<tr>
<td>Direct exocrine testing</td>
<td></td>
</tr>
</tbody>
</table>
| Dreiling tube and pancreatic stimulation with CCK, secretin, or Lundh meal | Invasive, poorly tolerated
| Endoscopic-assisted collection of pancreatic secretions following CCK or secretin stimulation | Invasive
| Indirect exocrine testing                 |                                              |
| Fecal elastase-1                          | Poor sensitivity for early/mild exocrine insufficiency |
| Secretin-enhanced MRI                     | Limited assessment                           |
| Serum/urine pancreolaury                  | Limited in patients with bile salt deficiency, celiac disease, renal failure, post-gastrectomy |
| $^{13}$C-mixed triglyceride breath testing  | Currently investigational use only           |
Indications for PERT in patients with documented PEI include weight loss, excretion of more than 15 g of fecal fat daily while consuming 100 g of fat per day, or steatorrhea-related relevant symptoms.15 Supplements should be taken with meals and throughout meals (not before meals), as well as with snacks (at 50% of typical dosing).13 Side effects of pancreatic enzymes are uncommon, and most patients tolerate these preparations well.46-48 However, high-dose PERT has been associated with rare cases of fibrosing colonopathy in some patients with CF.46-48

Recommendations for initial dosing and subsequent titration of PERT vary, with most suggesting 25,000 to 40,000 IU of PES per regular meal.15 The general principle is to start at the lowest dose and titrate upward to effect. Real-world plans should be based on individual clinician preference, package insert instructions, clinical symptoms, fecal fat quantitation, changes in weight, and the results of other tests.13,15,31 Several groups of investigators have proposed generic management algorithms for PERT (Figure 2),13 but more precise guidance from various medical societies would be of benefit.

Few head-to-head studies have compared efficacy and safety among PERT supplement types, and most of these products are indicated for the treatment of PEI due to CF or other conditions, but their labels do not specify dosing for the different conditions. However, one PES (Creon), which is indicated for PEI resulting from CP and pancreatectomy, as well as CF and other conditions, was studied in an RCT conducted in patients with PEI due to CP or pancreatectomy (N=54).49 The primary efficacy end point was the mean change in coefficient of fat absorption (CFA) from the run-in period to the end of the double-blind period; the mean changes in CFA were 32% for pancrelipase and 9% for placebo (P<0.0001). Subjects received pancrelipase at a dose of 72,000 IU lipase units per meal comprised of at least 100 g of fat.

Diarrhea despite PERT may be due to denaturation of lipase by gastric acid, improper timing of enzymes, coexisting small intestinal mucosal disease, rapid intestinal transit, noncompliance (especially in children and adolescents), alternate diagnosis (eg, PC, celiac disease), or motility disorders.13,31 In other cases, bacterial overgrowth may be responsible for refractory diarrhea.13,31 and decontamination of intestinal lumen with a course of antibiotics, supplementation of bile acids, and use of probiotics should be considered.

### Conclusion

Both CP and PC are serious conditions that can result in increased morbidity and mortality. PEI is a common consequence of both conditions and results in pain, steatorrhea, maligestion, malnutrition, and adverse cardiovascular outcomes. Diagnosis of PEI is achieved through clinical history, objective documentation of steatorrhea, and sometimes via direct or indirect functional

Table 3. FDA-Approved Pancreatic Enzyme Supplements46-48

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Product</th>
<th>Lipase</th>
<th>Protease</th>
<th>Amylase</th>
<th>Indications$^a$</th>
<th>Dosing$^b,c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancrelipase delayed-release capsules (enteric-coated minimicrospheres [0.71-1.60 mm]; Abbott Laboratories [formerly Solvay Pharmaceuticals])</td>
<td>Creon 6,000</td>
<td>6,000</td>
<td>19,000</td>
<td>30,000</td>
<td>PEI due to CF, CP, pancreatectomy, other conditions</td>
<td>500 lipase units/kg per meal ↑ to max 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg per day), or &lt;4,000 lipase units/g fat ingested per day</td>
</tr>
<tr>
<td></td>
<td>Creon 12,000</td>
<td>12,000</td>
<td>38,000</td>
<td>60,000</td>
<td>PEI due to CP, other conditions</td>
<td>For adults with PEI due to CP or pancreatectomy, individualize dosage based on clinical symptoms, degree of steatorrhea, fat content of diet</td>
</tr>
<tr>
<td></td>
<td>Creon 24,000</td>
<td>24,000</td>
<td>76,000</td>
<td>120,000</td>
<td>PEI due to CP, other conditions</td>
<td>For adults with PEI due to CP or pancreatectomy, individualize dosage based on clinical symptoms, degree of steatorrhea, fat content of diet</td>
</tr>
<tr>
<td>Pancrelipase delayed-release capsules (enteric-coated beads [1.8-2.25 mm]; Eurand Pharmaceuticals)</td>
<td>Zenpep 5</td>
<td>5,000</td>
<td>17,000</td>
<td>27,000</td>
<td>PEI due to CP, other conditions</td>
<td>500 lipase units/kg per meal ↑ to max 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg per day), or &lt;4,000 lipase units/g fat ingested per day</td>
</tr>
<tr>
<td></td>
<td>Zenpep 10</td>
<td>10,000</td>
<td>34,000</td>
<td>55,000</td>
<td>PEI due to CP, other conditions</td>
<td>For adults with PEI due to CP or pancreatectomy, individualize dosage based on clinical symptoms, degree of steatorrhea, fat content of diet</td>
</tr>
<tr>
<td></td>
<td>Zenpep 15</td>
<td>15,000</td>
<td>51,000</td>
<td>82,000</td>
<td>PEI due to CP, other conditions</td>
<td>For adults with PEI due to CP or pancreatectomy, individualize dosage based on clinical symptoms, degree of steatorrhea, fat content of diet</td>
</tr>
<tr>
<td></td>
<td>Zenpep 20</td>
<td>20,000</td>
<td>68,000</td>
<td>109,000</td>
<td>PEI due to CP, other conditions</td>
<td>For adults with PEI due to CP or pancreatectomy, individualize dosage based on clinical symptoms, degree of steatorrhea, fat content of diet</td>
</tr>
<tr>
<td>Pancrelipase delayed-release capsules (enteric-coated microtablets [2 mm]; McNeil Pediatrics/Ortho-McNeil-Janssen Pharmaceuticals)</td>
<td>Pancreaze 4</td>
<td>4,200</td>
<td>10,000</td>
<td>17,500</td>
<td>PEI due to CP, other conditions</td>
<td>500 lipase units/kg per meal ↑ to max 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg per day), or &lt;4,000 lipase units/g fat ingested per day</td>
</tr>
<tr>
<td></td>
<td>Pancreaze 10</td>
<td>10,500</td>
<td>25,000</td>
<td>43,750</td>
<td>PEI due to CP, other conditions</td>
<td>For adults with PEI due to CP or pancreatectomy, individualize dosage based on clinical symptoms, degree of steatorrhea, fat content of diet</td>
</tr>
<tr>
<td></td>
<td>Pancreaze 16</td>
<td>16,800</td>
<td>40,000</td>
<td>70,000</td>
<td>PEI due to CP, other conditions</td>
<td>For adults with PEI due to CP or pancreatectomy, individualize dosage based on clinical symptoms, degree of steatorrhea, fat content of diet</td>
</tr>
<tr>
<td></td>
<td>Pancreaze 20</td>
<td>21,000</td>
<td>37,000</td>
<td>61,000</td>
<td>PEI due to CP, other conditions</td>
<td>For adults with PEI due to CP or pancreatectomy, individualize dosage based on clinical symptoms, degree of steatorrhea, fat content of diet</td>
</tr>
</tbody>
</table>

$^a$ Package inserts refer to PEI as “exocrine pancreatic insufficiency.”
$^b$ Dosing for children ≥4 y and adults.
$^c$ Per-kg dosing refers to patient body weight.

**CP**, cystic fibrosis; **CF**, chronic pancreatitis; **max**, maximum; **PEI**, pancreatic exocrine insufficiency (package inserts refer to condition as exocrine pancreatic insufficiency.)
testing. Management of PEI consists of vitamin supplementation, oral PERT, and some degree of dietary modification. To date, 3 different PES have satisfied new regulatory requirements issued by the FDA to assure safety and consistency of therapeutic response. There are no definitive clinical recommendations to guide appropriate dosing and titration of PES; thus, clinical use is dependent on individual considerations and responses to therapy.

References