Exocrine Pancreatic Insufficiency

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Introduction

Exocrine pancreatic insufficiency (EPI) refers to insufficient secretion of pancreatic enzymes (acinar function) and/or sodium bicarbonate (ductal function), resulting in maldigestion and malabsorption of nutrients [1]. The symptoms and manifestations of EPI are largely due to an inability to digest fat. Symptoms are typically nonspecific but must be suspected in every child with steatorrhea (excess fat in the stool), failure to thrive of unexplained reasons, fat-soluble vitamin deficiency, as well as in children with recurrent pancreatitis [2] (see Chap. 34). References 3–29 constitute a comprehensive review of all known forms of EPI [3–29]. Table 39.1 lists both relatively common as well as rarer genetic causes of this condition.

EPI can also develop from nonpancreatic disorders [30]. In celiac disease, inflammatory bowel disease, or other conditions with proximal small-bowel mucosal inflammation, EPI can be caused by impaired release of secretin and cholecystokinin (CCK), which are potent stimulators of pancreatic secretion. Gastrointestinal surgery such as pancreatectomy, gastrectomy, small-bowel resections, or even esophagectomy may also result in EPI due to altered pancreatic enzymes and gastrointestinal hormone levels.

Exocrine Pancreatic Insufficiency in Cystic Fibrosis

Cystic fibrosis (CF) is the most common etiology of EPI in children. CF is an autosomal-recessive condition caused by defects in the cystic fibrosis transmembrane regulator (CFTR) gene. Although the severity of EPI is highly dependent on the specific genotypic mutation, about 85% of patients with CF develop EPI by 1 year of age [31].

Pathophysiology of Exocrine Pancreatic Insufficiency in Cystic Fibrosis

Mutations of the CFTR gene cause impaired chloride transport at the apical surface of epithelial cells [32] and disturb chloride-coupled bicarbonate transport [33] and sodium channel activity [34]. Pancreatic secretion of chloride, bicarbonate, sodium, and potassium in response to combined CCK and secretin stimulation is impaired in all patients with CF, regardless of pancreatic function status [35]. Bicarbonate secretion is most impaired, and defective electrolyte secretion leads to reduced fluid secretion [36]. Defective bicarbonate secretion results in impairment in the luminal flow of pancreatic enzymes and proenzymes and impairment in the trafficking of zymogen granules, leading to a severe block in acinar cell secretion followed by loss of cellular function, cell death, fibrosis, and eventual pancreatic insufficiency that leads to a decline in all the enzymes secreted by the pancreas [32, 36].

In healthy people, only 5–10% of the normal postmeal pancreatic enzyme output is adequate for normal digestion, indicating the large reserve capacity of the pancreas [32]. This reserve capacity means that clinically significant malabsorption is not evident until at least 90% of the exocrine cells of the pancreas are destroyed [37]. In normal individuals, the presence of free fatty acids in the proximal small bowel causes release of CCK, which in turn stimulates pancreatic secretion [38]. When pancreatic insufficiency begins to develop, this feedback loop is impaired and the site of maximal digestion shifts to the more distal bowel [32]. This results in larger amounts of nutrients being delivered to the distal bowel with changes in motor and secretory function of the more proximal bowel [39, 40]. These changes, in turn, lead to quicker intestinal transit and malabsorption [40].

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Table 39.1 Syndromes and genetic conditions associated with pancreatic insufficiency [3–29]

Condition	Affected gene(s)	Inheritance	OMIM	Reference
Cystic fibrosis	CFTR	AR	219,700	[3]
Shwachman–-Diamond syndrome	SBDS	AR	260,400	[4]
	DNAJC21	AR	617,052	[5]
	EFL1	AR	617,941	[6]
	SRP54	AD	618,752	[7]
Johanson–Blizzard syndrome	UBR1	AR	243,800	[8]
Pearson marrow-pancreas syndrome	Mitochondrial DNA defects		557,000	[9]
Jeune syndrome	ATD	AR	208,500	[10]
Pancreatic agenesis	PDX1	AR	260,370	[11]
	PTF1A	AR	615,935	[12]
Pancreatic agenesis and congenital heart defects	GATA6	AD	600,001	[13]
Pancreatic and cerebellar agenesis	PTF1A	AR	609,069	[14]
Congenital lipase deficiency	PNLIP	AR	614,338	[15]
Congenital enterokinase deficiency	PRSS7	AR	226,200	[16]
Hereditary pancreatitis			167,800	
Trypsin dependent	PRSS1	AD		[17]
	SPINK1	AD		[18]
	CTRC	AD		[19]
	CASR	AD		[20]
Trypsin independent	CFTR	AD		[21]
	CPA1			[22]
	CLDN2	X-linked		[23]
	MORC4	X-linked		[24]
	CELA3B	AD		[25]
Pseudohypoparathyroidism Type IA	GNAS1	AD	103,580	[26]
CoQ-responsive Oxphos deficiency	Unknown			[27]
Exocrine pancreatic insufficiency, dyserythropoietic anemia and calvarial hyperostosis	COX4I2	AR	612,714	[28]
Infantile-onset multisystem neurologic, endocrine, and pancreatic disease (IMNEPD)	PTRH2	AR	616,263	[29]

Abbreviations: *OMIM* Online Mendelian Inheritance in Man, *CFTR* cystic fibrosis transmembrane conductance regulator, *SBDS* Shwachman–Bodian–Diamond syndrome, *DNAJC21* DNAJ heat shock protein family (Hsp40) member C21, *EFL1* elongation factor like GTPase 1, *SRP54* signal recognition particle 54, *UBR1* ubiquitin protein ligase E3 component N-recognin 1, *ATD* asphyxiating thoracic dystrophy (chondroectodermal dysplasia-like syndrome), *PDX1* pancreatic and duodenal homeobox 1, *PTF1A* pancreas-associated transcription factor 1a, *GATA6* GATA-binding protein 6, *PNLIP* pancreatic lipase, *PRSS* serine protease, *SPINK1* serine peptidase inhibitor Kazal type 1, *CTRC* chymotrypsin C, *CASR* calcium-sensing receptor, *CFTR* cystic fibrosis transmembrane conductance regulator, *CPA1* carboxypeptidase A1, *CLDN2* claudin2, *MORC4* MORC family CW-type zinc finger 4, *CELA3B* chymotrypsin-like elastase 3B, *GNAS* GNAS complex locus, *COX4I2* cytochrome C oxidase subunit 4I2, *PTRH2* peptidyl-TRNA hydrolase 2, *AR* autosomal recessive, *AD* autosomal dominant

Whether a patient is pancreas sufficient (PS) or EPI has clinical and prognostic significance in CF. PS does not mean normal pancreatic function but that enough pancreatic function is present to avoid the need for pancreatic enzyme replacement therapy (PERT). Patients who are PS are more susceptible to pancreatitis [41], while EPI patients have more severe lung disease, malnutrition, and liver disease [42].

Shwachman–Diamond Syndrome

Shwachman–Diamond syndrome (SDS) is the second most common cause of EPI in children. SDS is an autosomal-recessive disorder characterized by congenital anomalies, pancreatic insufficiency, bone marrow failure, and predisposition to myelodysplasia and acute myeloid leukemia (AML) [43]. Mutations in the Shwachman–Bodian–Diamond syndrome (*SBDS*) gene on chromosome 7q11 can be found in approximately 90% of classically presenting patients with SDS [44]. The SBDS gene is involved in ribosomal function [45], and ribosomal subunit assembly is impaired in patients with SDS [46]. These mutations usually result in reduced, but not absent, protein expression. In mice, targeted deletion of the gene results in embryonic death, suggesting that some expression of this gene is necessary for survival [47]. The exact mechanism by which this leads to pancreatic insufficiency is unknown. One study found that patients negative for mutations in the SBDS gene may have more severe hematological manifestations while having milder pancreatic disease [48].

The incidence of SDS is 1:76,000 individuals with a male: female ratio of 1.7:1 [49, 50].

The classic presentation of SDS is in infancy with failure to thrive, diarrhea, and neutropenia. SDS infants have an

average birth weight at the 25th percentile [50]. Growth failure with malnutrition is common in the first year of life, and height velocity falls such that height remains below the third percentile in 38–56% of patients [51, 52]. After diagnosis, and with appropriate therapy, most children regain normal growth velocity, though height and weight remain below the third percentile [53]. Steatorrhea is caused by decreased secretion of pancreatic enzymes, while ductular fluid and electrolyte secretion of the pancreas remain normal [54, 55]. EPI tends to be diagnosed within the first 6 months of life with 90% of patients being diagnosed in the first year [54]. Spontaneous improvement in pancreatic function can occur in later childhood with 50% of patients by age 4 years having normal fat absorption and no longer requiring pancreatic enzyme supplementation [54]. The pancreas in SDS exhibits a characteristic fatty replacement, which can be visualized on ultrasound, CT, and, perhaps, best by MRI [56].

Hepatomegaly and raised serum liver enzymes are common in children with SDS [57]. These resolve by the age of 5 years, and no long-term consequences have been observed [57].

Neutropenia is the most common cytopenia and can be persistent, intermittent, or cyclic and may vary from mild to severe [50]. Anemia with low reticulocyte counts [50] and elevations in fetal hemoglobin are each seen in 80% of patients [58]. Thrombocytopenia can also be seen. Bone marrow biopsy is usually hypoplastic with increased deposition of fat [58, 59]. Patients with SDS have a propensity to developing infections due to the neutropenia and the occasional functional neutrophil deficits that are seen in SDS [60]. Patients with SDS develop clonal changes in the bone marrow, which may or may not be associated with an increased risk of myelodysplasia or acute myeloid leukemia (AML) [61]. Due to the predisposition to myelodysplasia and AML, all patients with SDS should be referred to a pediatric hematologist. Based on data from several registries, the frequency of both myelodysplasia and AML increases with increasing age [48, 62, 63]. Hematopoietic stem cell transplantation should be considered for treatment of severe pancytopenia, myelodysplasia, or AML [64].

The bony dysplasia of SDS manifests as short stature and delayed appearance but subsequent normal development of secondary ossification centers [50]. There is variable metaphyseal widening and irregularity that is most often seen in the ribs in early childhood and in femurs later in childhood and adolescence [65]. Rarely, skeletal involvement may be extremely severe and generalized [50]. Usually, these metaphyseal changes are clinically insignificant, but rarely, they may lead to limb deformities and fractures [65].

A characteristic pattern of neurocognitive and behavioral difficulties has been described in SDS [66].

A high degree of suspicion may be needed to diagnose milder cases of SDS. A study of 37 children with SDS found that neutropenia (81%), diarrhea (58%), failure to thrive (73%), lipomatous infiltration of the pancreas (~90%), low fecal elastase (82%), and skeletal (38%), congenital, and endocrine malformations (65%) were all inconsistently present [67].

Serum immunoreactive trypsinogen (IRT) and pancreatic isoamylase concentrations can be useful markers of the pancreatic phenotype in SDS [68]. In healthy children, serum IRT concentrations are at adult levels at birth, while pancreatic isoamylase concentrations are low at birth and reach adult levels by 3 years of age [68]. In contrast, in SDS, young children have low serum IRT concentrations, which then rise with age, while serum pancreatic isoamylase activities are low at all ages. Serum IRT is generally low in EPI patients with SDS, while a normal value does not rule out EPI. Serum isoamylase concentrations are not useful in determining PS or EPI. Hence, when SDS is suspected, a serum IRT should be obtained in children <3 years of age, while serum pancreatic isoamylase should be obtained in children ≥3 years of age [50].

The diagnosis of SDS is made using the criteria shown in Table 39.2. The combination of exocrine pancreatic dysfunction and hematological abnormalities when other known causes of exocrine pancreatic dysfunction and bone marrow failure are excluded gives rise to a clinical diagnosis of SDS [50]. CF should be ruled out with a sweat test, while Pearson syndrome can be differentiated by a bone marrow examination and imaging of the pancreas. Cartilage hair hypoplasia, which presents with diarrhea (but not with EPI), cytopenia, and metaphyseal chondrodysplasia, is more common in certain populations such as the Amish.

Exocrine Pancreatic Insufficiency in Chronic Pancreatitis

All children with chronic pancreatitis should be assessed for EPI at least annually and more often if symptoms develop in the interim. Children should be assessed for EPI using a stool elastase and should be considered EPI if the stool elastase <200 ug/g. EPI in children with chronic pancreatitis is managed in the same manner as EPI from any other cause.

Pearson Syndrome

Pearson syndrome (formerly Pearson Marrow-Pancreas syndrome) is a rare genetic condition with unknown prevalence. Pearson described a syndrome of refractory, transfusion-dependent sideroblastic anemia with vacuolization of the bone marrow and EPI [9]. Other variable features may include hepatic failure, proximal renal tubulopathy, watery diarrhea, patchy erythematous skin lesions, neutropenia, and thrombo-

Table 39.2 Diagnostic criteria for Shwachman–Diamond syndrome [50]

Clinical and molecular diagnostic criteria
Clinical diagnosis Fulfill the combined presence of hematological cytopenia of any given lineage (most often neutropenia) and exocrine pancreas dysfunction
Hematologic abnormalities may include the following: (a) Neutropenia <1.5 × 10^9/L on at least 2 occasions over at least 3 months (b) Hypoproductive cytopenia detected on 2 occasions over at least 3 months
Tests that support the diagnosis but require corroboration: (a) Persistent elevation of hemoglobin F (on at least 2 occasions over at least 3 months apart) (b) Persistent red blood cell macrocytosis (on at least 2 occasions over at least 3 months apart), not caused by other etiologies such as hemolysis or a nutritional deficiency
Pancreatic dysfunction may be diagnosed by the following: (a) Reduced levels of pancreatic enzymes adjusted to age [fecal elastase, serum trypsinogen, serum (iso)amylase, serum lipase]
Tests that support the diagnosis but require corroboration: (a) Abnormal 72-hr fecal fat analysis (b) Reduced levels of at least 2 fat-soluble vitamins (A, D, E, K) (c) Evidence of pancreatic lipomatosis (e.g., ultrasound, CT, MRI, or pathological examination of the pancreas by autopsy)
Additional supportive evidence of SDS may arise from the following: (a) Bone abnormalities (b) Behavioral problems (c) Presence of a first degree-family member diagnosed before with SDS
Other causes of pancreatic insufficiency should be excluded, in particular when the SBDS gene mutation analysis is negative
Molecular diagnosis: biallelic SBDS gene mutation Positive genetic testing for SBDS mutations known or predicted to be deleterious, e.g., from protein modeling or expression systems for mutant SBDS
Caveats: Many situations arise when molecular diagnosis is NOT confirmatory in the presence of clinical symptoms: No identified mutations (about 10% of cases) Mutation on one allele only Gene sequence variations that have unknown or NO phenotypic consequence A novel mutation, such as a predicted missense alteration, for which it is not yet possible to predict whether it is disease causing SBDS polymorphisms on one or both alleles. Large population studies may be needed to exclude a sequence polymorphism as a bona fide irrelevant variant

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cytopenia, and high serum lactate/pyruvate ratios [69]. This condition should be considered in the differential diagnosis of SDS. In this syndrome, vacuolization of the marrow is seen, while in SDS, the bone marrow is dysplastic; the pancreas is fibrotic in Pearson syndrome, while it is fatty in SDS [70]. Pearson syndrome is caused by large deletions or rearrangements in mitochondrial DNA, which are more abundant in the blood than in other tissues [69]. Diagnosis is suspected based on clinical findings and can be confirmed by Southern blot analysis, which detects rearrangements of mitochondrial DNA [71]. This syndrome is usually fatal in infancy, but some children who survive past infancy develop severe neurological symptoms such as proximal myopathy, seizures, ataxia, or abnormal movements, suggestive of another mitochondrial DNA disorder, Kearns-Sayre syndrome [72]. In children without multisystem involvement, bone marrow transplantation or unrelated cord blood cell transplantation has been suggested as a mechanism to manage the severe hematological manifestations of this syndrome [71].

Johanson–Blizzard Syndrome

Johanson–Blizzard syndrome (JBS) is a rare autosomal-recessive disorder caused by mutations in the *UBR1* gene on chromosome 15q15.2 [73, 74]. UBR1 encodes an E3 ubiquitin ligase that is involved in proteolysis [74]. However, the exact causative mechanism of EPI in JBS is unknown, but likely due to a near-total absence of pancreatic acini and replacement by fat. A small beak-like nose (due to aplasia or hypoplasia of the alae nasi) and EPI in early infancy are most consistently present, while other features in decreasing order of occurrence include dental anomalies, congenital scalp defects, sensorineural hearing loss, growth and psychomotor retardation, hypothyroidism, imperforate anus, and genitourinary anomalies [75].

Clinical Symptoms of Exocrine Pancreatic Insufficiency

The symptoms of fat malabsorption, which have been best described in CF, are abdominal pain, constipation, flatulence, and diarrhea [32]. Diarrheal symptoms are not different between PS and EPI patients in CF [32]. Hence, these symptoms are not good markers of EPI and definitely not measures of adequacy of PERT.

EPI can result in significant malnutrition and nutritional deficiencies, particularly of fat-soluble vitamins A, D, E, and K [76]. Zinc, iron, calcium, folic acid, magnesium, and selenium deficiencies have been described in CF [76, 77]. In CF, the presence of liver disease and enteropathic changes may create further nutritional issues.

Diagnosis of Exocrine Pancreatic Insufficiency

The ideal test of pancreatic function should be specific, non-invasive, able to quantitate pancreatic function, able to indicate the need and the appropriate dosage of substitutive enzymes even during therapy, cost-effective, and broadly available [78]. No such test is presently available [78]. Tests

Table 39.3 Exocrine pancreatic function tests

Direct tests	Indirect tests
Nonstimulatory test Fecal elastase-1 Fecal chymotrypsin Immunoreactive trypsinogen (IRT), lipase, and isoamylase levels	Spot fecal fat[a] Steatocrit[a] 72-hour fecal fat excretion test ^{13}C-labeled mixed-triglyceride breath test
Stimulatory test Secretin stimulation test Cholecystokinin stimulation test Secretin-cholecystokinin stimulation test	

[a]Not recommended

for EPI can be performed by measuring pancreatic secretion (direct tests) or by estimating the consequences of malabsorption (indirect tests) [1]. Common tests for EPI are summarized in Table 39.3.

Indirect Pancreatic Function Tests

The standard indirect pancreatic function test measurement of fat absorption is the 72-hour fecal fat excretion test. The coefficient of fat absorption (CFA) is calculated as follows:

((Fat ingestion – Fat excretion) / Fat ingestion) × 100(%). Normal CFA values are >85% in infants <6 months of age, and >95% in older children. During this time, stool is collected while consuming a standardized high-fat diet or more typically ingestion is recorded in a detailed food diary [79]. Microscopic examination of a spot stool sample using Sudan stain to detect fat droplets or the acid steatocrit is not recommended due to their lack of sensitivity and specificity.

The ^{13}C-labeled mixed-triglyceride breath test (^{13}C -MTG) is a noninvasive method of assessing lipase activity [80, 81]. Orally administered ^{13}C-labeled fatty substrates are digested by the pancreatic lipase; the released free fatty acids or monoglycerides are absorbed in the gut and oxidized in the liver to $^{13}CO_2$, which is rapidly exhaled in breath and can be measured. Several studies have shown a good correlation of ^{13}C -MTG and fecal fat quantification, with high sensitivity and specificity for the diagnosis of EPI [82, 83]. ^{13}C -MTG can also be used to assess the efficacy of PERT.

The disadvantages are the unavailability of the test in the United States, variability of test protocol, and the age limit as younger patients may not be able to follow the testing instructions. The test results can be influenced by other conditions such as liver disease, gastrointestinal dysmotility, and lung disease.

Direct Pancreatic Function Tests

Fecal elastase-1 is the most commonly used test to diagnose EPI. The test, although called fecal elastase-1, does not actually measure elastase-1 as this is transcriptionally silenced in humans. The test actually measures chymotrypsin-like elastases (CELA) 3A and 3B [77]. These enzymes are secreted by the pancreas and do not undergo degradation in the gut. The monoclonal fecal elastase-1 test only identifies the human form of the enzymes; hence, the test can be done even when the patient is receiving porcine-derived PERT [84]. It is inexpensive with good sensitivity and specificity for detection of EPI. The sample needs a very small amount of stool (≥1 gram) and is stable for weeks at room temperature [85]. Falsely low values may be obtained when the stool is dilute as in any diarrheal illness or in the presence of enteropathies.

After 2 weeks of age, PS patients can be differentiated from EPI patients using a cut-off of 200 μg/gram [86], whereas others have suggested that 180 μg/gram is a more accurate cut point in patients with CF [87]. Fecal elastase-1 can also be used in the annual monitoring of CF patients with PS to identify the onset of EPI.

In patients with CF, the presence of a low fecal elastase-1 is usually considered diagnostic of EPI despite the fact that fecal elastase-1 correlates poorly with fecal fat excretion [88]. In other conditions, especially in children who present with poor growth or malabsorption, the next steps after obtaining a fecal elastase-1 level are less clear. Also, preliminary reports suggest that drugs regulating CFTR (e.g., ivacaftor) may increase fecal elastase-1 and potentially convert children with EPI to PS; however, more data are needed to confirm these findings [89–92].

The CF Foundation recommends an evaluation of pancreatic functional status by fecal elastase or coefficient of fat absorption for all children with CF under 2 years of age [93]. Fecal elastase should be repeated at age 1 year in children diagnosed with EPI in infancy, especially in those with an initial fecal elastase value of >50 μg/gram to ensure that those with a falsely low fecal elastase value do not receive PERT unnecessarily [85].

Fecal chymotrypsin is a less sensitive and specific marker of pancreatic function than fecal elastase-1. However, this test, which does identify porcine enzymes, can be used to monitor compliance to PERT in patients who are known to be EPI [94].

Serum IRT of less than 20 ng/mL is specific for EPI [95]. Serum IRT levels, as a part of newborn screen, are at adult levels at birth in healthy newborns, but markedly elevated in newborns with CF regardless of whether their mutation is pancreatic sufficient or insufficient [96, 97]. Serum IRT levels are generally reduced later in life in patients with EPI, but a normal value does not rule out EPI.

Stimulatory tests or direct pancreatic function tests using secretagogues such as CCK and/or secretin are currently considered the gold standard to evaluate EPI. Unlike indirect pancreatic function tests, this assay can evaluate contents of pancreatic fluids and differentiate EPI from specific pancreatic enzyme deficiencies.

The original test performed by using Dreiling tubes was time-consuming and poorly tolerated by patients, so it has been replaced by an endoscopic method [98, 99]. Either secretin or CCK is administered intravenously prior to endoscopic intubation. Within 10 minutes, pancreatic fluid is collected from the duodenum (close to the ampulla of Vater). The pancreatic fluid can be evaluated for pH, protein content, amylase, lipase, trypsin, chymotrypsin, elastase, and electrolytes including bicarbonate [100].

The pancreatic stimulation test appears to be one of the most sensitive tests for the diagnosis of severe chronic pancreatitis and EPI, but it is less sensitive in less advanced disease. False abnormal results may be reported in patients with diabetes, celiac sprue, advanced liver disease, or those with a recent episode of acute pancreatitis [101].

Pancreatic stimulation testing may be performed with the use of a magnetic resonance cholangiopancreatography (MR PFT) to help assess pancreatic anatomy and quantify exocrine pancreatic function. Adult data support the use of MR PFT as a noninvasive and radiation-free method. However, a standardized protocol with an exact interpretation of findings needs to be developed for use in children [102, 103].

Management

Much of the data on management of pancreatic insufficiency in children is extrapolated from CF. In general, the symptoms of pancreatic insufficiency can be more easily controlled in conditions other than CF than in CF. PERT remains the mainstay of treatment for patients with clinical symptoms of pancreatic insufficiency or laboratory signs of malabsorption in CF and non-CF EPI [104]. In CF, PERT is indicated in all infants with two CFTR mutations associated with EPI [93]. FDA-approved PERT are summarized in Table 39.4. All PERT products are of porcine origin and con-

Table 39.4 FDA-approved pancreatic enzyme products

	Dosages available (lipase/protease/amylase units)	Bead/ microsphere diameter (mm)	Notes
Creon ®	3000/9500/15,000 6000/19,000/30,000 12,000/38,000/60,000 24,000/76,000/120,000 36,000/114,000/180,000	0.7–1.6	Oral, delayed release capsules
Pancreaze ®	2600/6200/10,850 4200/14,200/24,600 10,500/35,500/61,500 16,800/56,800/98,400 21,000/54,700/83,900	2	Oral, delayed release capsules
Pertyze ®	4000/15,125/14,375 8000/28,750/30,250 16,000/57,500/60,500 24,000/86,250/90,750	0.8–1.4 for 4000; 0.8–2.2 for others	Oral, delayed release capsules with bicarbonate-buffered enteric-coated microspheres
Ultresa ®	13,800/27,600/27,600 20,700/41,400/41,400 23,000/46,000/46,000	2.0–2.4	Oral, delayed release capsules approved for use in >12 months plus a weight requirement
Viokace ®	10,440/39,150/39,150 20,880/78,300/78,300	N/A	Nonenteric-coated tablets Approved only for use in adults Must be given with a proton pump inhibitor
Zenpep ®	3000/10,000/14,000 5000/17,000/24,000 10,000/32,000/42,000 15,000/63,000/47,000 20,000/63,000/84,000 25,000/79,000/105,000 40,000/126,000/168,000	1.8–1.9 for 3000 and 5000; 2.2–2.5 for others	Oral, delayed release capsules
Relizorb ®	Only contains lipase 1 cartridge per 500 mL of enteral formula, up to 2 cartridges per day	Unknown	Use with soluble fiber containing enteral feeding only

Creon® [package insert]. North Chicago, IL: Abbott Laboratories; 2020
Pancreaze® [package insert]. Titusville, NJ: Janssen Pharmaceuticals Inc.; 2018
Pertyze® [package insert]. Bethlehem, PA: Digestive Care Inc.; 2017
Ultresa® [package insert]. Birmingham, AL: Aptalis Pharma US Inc.; 2012
Viokace® [package insert]. Birmingham, AL: Aptalis Pharma US Inc.; 2012
Zenpep® [package insert]. Madison, NJ: Allergan Therapeutics LLC.; 2020
Relizorb® [package insert]. Newton, MA: Alcresta Inc.; 2014

tain a mixture of the digestive enzymes, lipase, protease, and amylase in varying proportions. However, because lipase plays the main role in therapy, PERT dosage is based on the content of lipase units [104].

Enzyme dosing can be based on body weight (units of lipase/kg per meal) or the amount of fat present in the food (units of lipase/grams of fat eaten), but dosing based on body weight is more practical. In infants with CF, PERT doses are generally 2000–4000 lipase units per 120 mL of formula or per breast-feeding. In all other patients with EPI, the dose is gradually adjusted based on weight gain and absorption to a maximum of 2500 lipase units per kilogram per meal (not to exceed 10,000 lipase units/kilogram per day or 4000 units lipase/ gram dietary fat per day) [105]. Higher doses have been associated with fibrosing colonopathy and are not recommended [106]. Other side effects of PERT include soreness in the mouth and perianal irritation [107]. Allergies may occur due to the porcine origin of the enzyme preparations [107]. Hyperuricemia which was seen with older preparations is rarely seen now [108]. A sudden introduction of PERT to patients with uncontrolled fat malabsorption may lead to severe constipation with accompanying abdominal pain [107].

Enteric-coated microspheres or mini-microspheres of <2 mm in size are the preparations of choice for PERT. The efficacy data of micro- or minitablets of 2.2–2.5 mm in size is limited. In infants, the enzyme microspheres are mixed with a small amount of breast milk or infant formula or soft, acidic food with a pH of less than 4.5 such as applesauce and given via spoon immediately before the feed. In older children, the enzyme should be distributed to a full dose with main meals, and half that dose with snacks. Enzymes should either be given at the beginning of the meal or given half at the beginning and half midway through the meal, particularly if the feeding time is longer than half an hour. The capsules should be swallowed whole without crushing or chewing at as early an age as possible. In a tube-fed patient, PERT in a cartridge form can be connected directly to the enteral feeding pump.

Dietary fat restriction and very high-fiber diets should be avoided in children in EPI (CF and non-CF). Small, frequent, high-energy meals are recommended. However, some children with poor growth, particularly with CF, may not respond to high-calorie foods and oral high-calorie beverages. These children may be candidates for supplemental nocturnal gastrostomy tube feeding. In these patients, pancreatic enzymes should be given before and after the tube feeding or a digestive-enzyme cartridge that can be connected to the enteral feeding system can be used and has been shown to be effective in children with CF. While a polymeric formula is typically used, some children may require a protein hydrolysate formula due to uncontrolled malabsorption or poor growth despite adequate caloric intake. In children receiving the maximum dose of PERT, additional benefit may be obtained by the addition of zinc supplementation (1 mg elemental zinc/kg per day) [93] or acid-blockade medications (proton pump inhibitor) to prevent deactivation of enzymes by reducing luminal acidity. Other causes of malabsorption should be considered if no improvement is observed with all these strategies.

The efficacy of PERT can be observed by the improvement of malabsorptive symptoms such as steatorrhea, bloating, or poor weight gain and the nutritional status of the patients. However, there is no correlation between PERT dose and symptoms [32]. If no improvement is observed, a repeat quantitative fecal fat estimation with PERT or fecal chymotrypsin might be helpful.

In children with CF, CF-specific vitamin preparations are recommended. These vitamin preparations as well as the regular assessments of vitamin status should be considered in all children with pancreatic insufficiency. All patients with EPI should have measurement of fat-soluble vitamins (A, D, E, and K) at diagnosis and then every 6–12 months or every 3 months after a change in vitamin therapy [109]. It is recommended that these vitamins be taken with a fat-containing meal along with PERT. Monitoring of other vitamins, minerals, or trace elements is not routinely recommended unless deficiencies are clinically suspected.

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