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REVIEW

# Exocrine Pancreatic Insufficiency in Children – Challenges in Management

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**Abstract:** Cystic fibrosis (CF) is the leading etiology for exocrine pancreatic insufficiency (EPI) in children, followed by chronic pancreatitis, Shwachman-Diamond syndrome, and other genetic disorders. Management of EPI in children poses several unique challenges such as difficulties in early recognition, lack of widespread availability of diagnostic tests and limited number of pediatric-specific pancreatic centers. Pancreatic enzyme replacement therapy is the cornerstone of EPI management and in young children difficulties in administering pancreatic enzymes are frequently encountered. Patients with EPI also should be screened for fat-soluble vitamin deficiencies and receive appropriate supplementation. Among disorders with EPI in children, CF is the relatively well-studied condition, and most management recommendations for EPI in children come from expert consensus and conventional practice guidelines. The impact of EPI can be greater in children given their high metabolic demands and rapid growth. Early diagnosis and aggressive management of EPI prevent consequences of complications such as malnutrition, fat-soluble vitamin deficiencies, and poor bone health and improve outcomes. Management by multi-disciplinary team is the key to success.

**Keywords:** exocrine pancreatic insufficiency, EPI, children, PERT, pancreatic enzymes

## Introduction

Exocrine pancreatic insufficiency (EPI) is defined as inadequate secretion of pancreatic enzymes (function of acini) and/or sodium bicarbonate (ductal function) resulting in suboptimal gastrointestinal (GI) absorption of nutrients.[1] Pancreas has a huge functional reserve and frank steatorrhea does not occur until approximately 90% of pancreatic tissue is destroyed with pancreatic enzymes reduced to 5–10% of normal physiological quantities.[2,3] Even though the pancreas participates in the digestion of all macronutrients, lipase is predominantly affected in EPI resulting in impaired absorption of fat and fat-soluble vitamins.[2] In the early stages, EPI can be difficult to diagnose due to its rarity and non-specific GI symptoms.

The common causes of EPI in adults include chronic pancreatitis, cystic fibrosis (CF), diabetes mellitus, inflammatory bowel disease (IBD), and pancreatic cancer.[1,4–7] EPI in adults is relatively well described and various societal guidelines exist for EPI management in adults.[8–11] Even though there are many similarities in EPI between children and adults, there are key differences in the etiology and also specific challenges exist in managing EPI in young children. Cystic fibrosis (CF) is the most common and well-studied condition causing EPI in children and most treatment recommendations for EPI are inferred from expert consensus-based CF management guidelines. Outside CF, manifestations of EPI may be difficult to recognize due to its rarity, and limited availability of pediatric-specific pancreatic centers. There is also paucity of high-quality literature regarding management of EPI in this population.

In this review, we detail all the disorders which present with EPI during infancy and childhood and their management. We also highlight the challenges involved in the diagnosis of EPI in the pediatric age group with specific focus on the difficulties encountered in the administration of pancreatic enzyme replacement therapy (PERT) in children.

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# Causes of EPI

## Primary Causes of EPI

EPI could be primary with decreased pancreatic parenchyma or secondary to non-pancreatic causes. Primary pancreatic causes include several genetic syndromes or chronic pancreatitis resulting in pancreatic parenchymal loss of volume and function. After CF, chronic pancreatitis and Shwachman-Diamond syndrome (SDS) are the known primary causes of EPI in children.[12–14] Other genetic syndromes such as Johanson-Blizzard syndrome (JBS), Pearson-marrow syndrome, Jeune syndrome, pancreatic aplasia/hypoplasia, and deficiency of isolated pancreatic enzymes are rarely encountered[13,15,16] (Table 1 and Table 2). Unlike adults, pancreatectomy for treatment of pancreatic neoplasia resulting in EPI is relatively uncommon in children.[12]

## Secondary Causes of EPI

Secondary pancreatic insufficiency could result from lower stimulation of pancreatic secretions in duodenal mucosal inflammatory disorders such as refractory celiac disease or IBD with duodenitis, which may result in reduced release of cholecystokinin (CCK) from the damaged intestinal cells[2,14] (Table 1). Other causes of secondary pancreatic insufficiency include inappropriate mixing of pancreatic secretions with intestinal contents in conditions such as surgeries involving the upper gastrointestinal tract or inactivation of pancreatic lipase and colipase due to excessive acidity of the intestinal contents (Table 1).

Transient pancreatic insufficiency, a relatively poorly understood entity, is noted in severe malnutrition, post-viral infection state, or after pancreatic trauma.[91,92] A decrease in pancreatic amylase and lipase activities is often encountered

**Table 1** Causes of Exocrine Pancreatic Insufficiency in Children

| |
|---|
| **Primary Pancreatic Disorders** |
| • **Genetic syndromes** |
| Cystic fibrosis* |
| Shwachman Diamond syndrome* |
| Johanson-Blizzard syndrome |
| Pearson marrow-pancreas syndrome |
| Jeune syndrome |
| Pancreatic aplasia/hypoplasia |
| Deficiency of isolated pancreatic enzymes |
| • **Chronic pancreatitis*** |
| Hereditary pancreatitis (mutations in *PRSS1, CFTR, SPINK1, CTRC*) |
| Obstructive causes such as pancreas divisum, sphincter of Oddi dysfunction, gallstones |
| Drug-induced pancreatitis |
| Toxic/metabolic causes |
| Autoimmune pancreatitis |
| • **Surgical resection** |
| For pancreatic tumors or chronic pancreatitis |
| **Secondary Pancreatic Disorders** |
| • **Duodenal inflammatory conditions resulting in reduced cholecystokinin or secretin** |
| Inflammatory bowel disease |
| Celiac disease |
| • **Postcibal asynchrony between pancreatic enzyme delivery and intestinal chyme** |
| Upper gastrointestinal surgeries |
| • **Excessive gastric acidity inactivating pancreatic lipase** |
| Zollinger-Ellison syndrome |
| • **Transient pancreatic insufficiency** |
| Malnutrition, after a viral illness, abdominal trauma, maturation delay in infants |

**Note**: * relatively common causes of primary exocrine pancreatic insufficiency in children.

**Table 2** Inherited Syndromes Which Causes Exocrine Pancreatic Insufficiency During Infancy:[15,21]

| Genetic Conditions with OMIM | Gene/Locus | Inheritance | Approximate Incidence | Salient Features | References |
|---|---|---|---|---|---|
| Cystic fibrosis 219,700 | *CFTR* in chromosome 7q | Autosomal recessive | 1 in 3000–4000 live births in Caucasians | CF was first described by Dorothy Andersen in 1938. It is the most common lethal genetic condition in Caucasians with approximately 30,000 patients live in the US. In developed countries, more than 90% of CF are diagnosed by newborn screening. Most countries utilize serum immunoreactive trypsinogen (IRT) and/or genetic analysis for CF newborn screening. Confirmation of diagnosis is by sweat testing and can be done after 6 weeks of age. Approximately 2000 mutations have been identified, and about 85% of patients have at least one copy of F508del. *CFTR* gene encodes the Cystic Fibrosis Transmembrane Regulator Protein (CFTR). CFTR is expressed in various epithelial cells such as respiratory cells, pancreatic ducts, intestinal cells, biliary tract, sweat duct, and vas deferens which results in multisystem involvement in CF. Before the advent of newborn screening, most patients with CF were diagnosed based on clinical presentations such as meconium ileus, poor growth, rectal prolapse, steatorrhea, and recurrent pulmonary infections. Meconium ileus occurs in approximately 15% of newborns with CF. Fecal elastase-1 is used to confirm EPI in infants newly diagnosed infants with CF, monitor pancreatic sufficient CF patients (during annual evaluation or if they develop manifestations of EPI), and evaluate older CF patients at the time of diagnosis. | [13,18–31] |
| Shwachman-Diamond syndrome 260,400 | *SBDS* in chromosome 7q11 | Autosomal recessive | 1 in 76, 000 | SDS was first described by Shwachman et al in 1964. SDS is the second most common inherited syndrome causing EPI after CF. SDS is characterized by multisystem involvement including the bone marrow failure, predisposition to infections, and hematologic malignancies, pancreatic lipomatosis, skeletal anomalies, and failure to thrive. About 90% of patients with a classic presentation of SDS have mutations in the Shwachman-Bodian-Diamond (*SBDS*) gene which codes for the SBDS protein. This protein is postulated to play a vital role in ribosomal maturation (60S subunits) and proliferation of cells. The most likely underlying biochemical mechanism is a complex IV defect leading to defective oxidative phosphorylation and endoplasmic reticulum stress. | [32–43] |

(*Continued*)



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**Table 2** (Continued).

| Genetic Conditions with OMIM | Gene/Locus | Inheritance | Approximate Incidence | Salient Features | References |
|---|---|---|---|---|---|
| Johanson-Blizzard syndrome 243,800 | *UBR1 in* chromosome 15q15.2 | Autosomal recessive | 1 in 250,000 | JBS was first described by Johanson and Blizzard in 1971. The *UBR1* (*ubiquitin protein ligase E3 component* N-[81]recognin 1) gene encodes one of at least four functionally overlapping E3 ubiquitin ligases of the N-end rule pathway, a conserved proteolytic system whose substrates include proteins with destabilizing N-terminal residues 20. *UBR1* is involved in controlling cellular proliferation and leucine-m-TOR signaling pathway and this resulting genetic imbalance is associated with dysregulated apoptosis resulting in a variety of development anomalies including pancreatic lipomatosis. Alae nasi hypoplasia or aplasia, scalp defects (cutis aplasia), hearing impairment, dental anomalies, microcephaly, cardiac anomalies, hypothyroidism, imperforate anus, and urogenital defects along with EPI (pancreatic lipomatosis) are noted in JBS. Severe growth and developmental delay are often noted. | [44–52] |
| Pearson's marrow-pancreas syndrome 557,000 | Mitochondrial DNA | Mitochondrial inheritance | Unknown (About 100 cases have been reported) | Pearson-marrow pancreas syndrome or Pearson-marrow syndrome was originally described in 1979 by Pearson. This syndrome is due to deletions of mitochondrial DNA resulting in defective oxidative phosphorylation. The most characteristic features include depressed hematopoietic cell lines (either singly or in combination). Sideroblasts are noted in ~50% of cases with ringed sideroblasts and cell vacuolization in the bone marrow. Characteristic features include depressed hematopoietic cell lines (either singly or in combination). Sideroblasts are noted in ~50% of cases with ringed sideroblasts and cell vacuolization in the bone marrow. EPI is noted in half the patients and the pancreas is usually fibrotic. Majority of deaths were attributed to multi-organ failure, metabolic acidosis, and severe infections. | [53–58] |
| Jeune asphyxiating thoracic dystrophy 208,500 | Multiple genes implicated in chromosome 15q13 | Autosomal-recessive | 1:100,000–1:130,000 live births | Jeune syndrome or asphyxiating thoracic dystrophy was first described in 1955. The phenotype of Jeune syndrome is variable. It is characterized by musculoskeletal abnormalities including a small, narrow chest leading to respiratory distress and, short-limbed dwarfism. EPI is due to pancreatic fibrosis. Renal abnormalities (cystic dysplasia/nephronophthisis), hepatic and pancreatic fibrosis, and ocular complications may occur later in life. Multiple musculoskeletal manifestations of varying severity such as abnormalities of the thorax, short-limbed dwarfism, and cystic dysplasia/ nephronophthisis of the kidneys are also noted. | [16,59–62] |

| | | | | | |
|---|---|---|---|---|---|
| Pancreatic agenesis 260,370 | *PDX1 gene* (codes for insulin promoter factor-1 IPF1) in chromosome 13q12.2 | Autosomal recessive | Unknown | Diabetes and EPI have been noted with onset in neonates with variable severity. | [51,63–67] |
| Pancreatic and cerebellar agenesis 609,069 | *PTF1A gene* in chromosome 10p12 | Autosomal recessive | Unknown | Pancreatic and cerebellar agenesis, diabetes mellitus | [68–70] |
| Pancreatic agenesis and congenital heart defects 600,001 | Heterozygous mutations in *GATA6 gene* in chromosome 18q11.2 | Autosomal dominant | Unknown | EPI, congenital heart defects, and diabetes mellitus | [71–73] |
| Syndrome of EPI, dyserythropoietic anemia, calvarial hyperostosis 612,714 | *COX412* in chromosome 20q11.21 | Autosomal recessive | Unknown | EPI, dyserythropoietic anemia, and calvarial hyperostosis | [74] |
| Congenital pancreatic lipase 614,338 | *PNLIP* in chromosome 10q25.3 | Autosomal recessive | Unknown | Chronic diarrhea and steatorrhea and malnutrition | [75–81] |
| Congenital pancreatic colipase 120,105 | *CLPS* in chromosome 6p21.21* | Unknown | Unknown | Chronic diarrhea and steatorrhea | [16,78,80,82,83] |
| Congenital trypsinogen deficiency 614,044 | *PRSS1* in chromosome 7q35* | Unknown | Unknown (few cases reported) | Failure to thrive, diarrhea, hypoproteinemia, and peripheral edema | [84–86] |
| Congenital enteropeptidase 226,200 | *TMPRSS15/PRSS7* in chromosome 21.q21.1 | Autosomal recessive | Unknown (few cases reported) | Even though in a strict sense, this condition is not an EPI, this brush border enzyme activates pancreas-derived zymogens in the small bowel. This disorder is characterized by severe protein malabsorption in early infancy, with growth faltering, chronic diarrhea (no steatorrhea), and anasarca. Adults may have mild symptoms, even after stopping pancreatic enzyme supplementation. | [87–89,148] |

**Note**: *Not documented in clinical cases.

**Abbreviations**: CF, cystic fibrosis; EPI, exocrine pancreatic insufficiency; JBS, Johanson-Blizzard syndrome; OMIM, Online Mendelian Inheritance in Man; SDS, Shwachman Diamond syndrome.



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in infants likely due to maturational delay of the digestive system and may not cause any symptoms of malabsorption as the lipase present in breast milk and salivary amylase have compensatory activities.[93,94]

## Clinical Presentation of EPI

Steatorrhea is noted in severe EPI and is usually reported by caregivers as bulky, malodorous, oily stools in the infant's diaper.[13] Similar to adults, older children and adolescents may manifest steatorrhea as large bulky, oily stools, which may be difficult to flush. Other symptoms of EPI include chronic loose stools, weight loss or poor weight gain, voracious appetite, bloating, and excessive flatulence.[17] Malnutrition and poor bone health are also frequently encountered.[95] In patients with undiagnosed EPI or patients without fat-soluble vitamin supplementation, deficiencies of fat-soluble vitamins (A, D, E, and K) can also be noted.[15] In the early stages, EPI is difficult to diagnose due to rarity and non-specific GI symptoms. As children are actively growing, EPI has more severe consequences with significant impairment on growth. Also, the symptoms of EPI overlap with other GI conditions resulting in malabsorption such as celiac disease, inflammatory bowel diseases, small intestinal bacterial overgrowth and giardiasis. The constellation of EPI symptoms and extra-pancreatic manifestations in other genetic conditions may help prompt the clinician for an EPI workup (Table 2).

## Diagnosis of EPI

### Indirect Pancreatic Function Tests

Pancreatic function tests are widely classified as indirect or direct tests (Table 3). Indirect tests are mostly stool-based, noninvasive, and less reliable in the early stages of EPI. Fecal fat screening by Sudan red staining (>2.5 droplets/high-

**Table 3** Pancreatic Function Tests

| Name of the Test | Comments Regarding Their Utility in Children |
|---|---|
| **Indirect tests - Noninvasive tests, simple to administer** | |
| Fecal elastase-1 (monoclonal) | Qualitative and easy to obtain. Lower sensitivity in early EPI and false-positive result if the stool is watery loose. This test should be repeated with formed stools. |
| Fecal chymotrypsin | Less sensitive than fecal elastase-1. PERT should be discontinued prior to testing. On the contrary, this test can be utilized to check PERT compliance. |
| 72-hour fecal fat estimation (co-efficient of fat absorption) | Gold standard test fat malabsorption. But nonspecific for EPI. Provides quantitative assessment of fecal fat absorption; can assess the adequacy of pancreatic enzyme replacement therapy. The 72-hour collection of stools is cumbersome and unpleasant. Requires detailed diet records to assess fat intake. |
| $^{13}$C-mixed triglyceride breath test | Not widely available in all countries and limited data in children. May pose challenges to administer in infants and young children. |
| IRT | Plasma IRT is elevated in CF infants and this is utilized in CF newborn screening test. Upon developing pancreatic insufficiency, IRT levels fall below normal around 6–7 years of age. Beyond CF newborn screening, serum IRT or trypsin is not useful for evaluating pancreatic status due to lack of specificity for EPI. |
| **Direct tests (Based on stimulation of pancreatic secretions)** | |
| Dreiling tube test | Old fashion test - performance is cumbersome in children and outdated in current practice. |
| Endoscopic pancreatic function tests | Performed in lieu of the Dreiling tube test. The need for anesthesia and endoscopy limits its widespread availability to tertiary pediatric centers. |
| Secretin-enhanced magnetic resonance cholangiopancreatography | Need for anesthesia in young children. Limited availability in tertiary pediatric centers. Also needs radiologists with pediatric pancreatology expertise. Limited data in the pediatric population. |

**Abbreviations**: CF, cystic fibrosis; EPI, exocrine pancreatic insufficiency; IRT, Immunoreactive trypsinogen; PERT, pancreatic enzyme replacement therapy.

power field) involves microscopic analysis of fecal fat. This test is not recommended as it is nonspecific for EPI and can be positive in other causes of malabsorption or as a result of rapid gut transit in young children.[17]

Co-efficient of fat absorption (CFA) is the gold standard test for fat malabsorption which is defined as the ratio between ingested fat minus excreted fat in the stool)/ingested fat and expressed as a percentage.[12] Normal value of CFA for patients older than 6 months of age is ≥93%, whereas in infants less than 6 months of age, ≥85% is normal[92,96,97] This difference in CFA in young infants is due to mild physiologic reduced intestinal fat absorption due to delay in maturation. This test should be performed on a defined fat diet and a 72-hour stool fat collection with strict documentation of intake and stools excreted.[12] A high-fat diet consisting of 100 g of fat per day is recommended for adolescents and adults and 2 g/kg in younger children.[17] This test is not specific for EPI but will be positive in any condition involving fat malabsorption.[13] CFA testing is cumbersome to perform, stool sample collection is unpleasant for patients and families and, a strict log of fat intake is time-consuming.[13]

Fecal elastase-1, an ELISA-based test for the human enzyme, is often useful to screen for EPI and has utility under selective circumstances. Compared to CFA, fecal elastase-1 has lower sensitivity (~25%) but higher specificity (96.4%) for EPI.[98,99] Stool sampling for elastase-1 testing is commonly used because it is non-invasive. The assay tests for human elastase, whereas pancreatic enzyme replacement therapy (PERT) products are porcine-based, so patients can continue taking PERT even when repeating elastase testing. Fecal elastase-1 <200 μg/gm of stool is indicative of EPI. A value of 100–200 μg/gm is classified as mild to moderate EPI, and <100 μg/gm is indicative of severe EPI and associated with steatorrhea.[100,101] Reducing the cutoff from 200 to 100 μg/gm increases the specificity of EPI but lowers the sensitivity.[102] A solid or semi-solid stool should be used to quantify fecal elastase-1 to avoid a false positive test for EPI resulting from stool dilution. Fecal elastase-1 is not helpful if isolated with enzyme deficiency is suspected.[98,99]

$^{13}$C-mixed triglyceride breath test is noninvasive but is not commonly available in all countries and is also challenging to administer in infants and young children.[17,103]

### Direct Pancreatic Function Tests

Direct (stimulatory) pancreatic function tests such as classical double-balloon Dreiling tube (oroduodenal tube) test are rarely performed in children due to their invasiveness, discomfort, and radiation. More frequently, endoscopic testing with CCK or secretin stimulation is performed.[2,92,98,104] Direct tests have higher sensitivity and specificity but are expensive and not available at all centers. Here, measurement of pancreatic enzymes and bicarbonate via endoscopic collection and testing can be done but mostly at tertiary centers. The testing should be carefully interpreted (isolated enzyme deficiency) in children younger than two years of age as enzyme activities mature with age.[105]

### Radiological Tests

Ultrasound is often the first radiological test used to evaluate the pancreatic anatomy but computer tomography (CT), or magnetic resonance cholangiopancreatography (MRCP), specifically secretin-enhanced MRCP, are more helpful to better delineate the pancreatic anatomy such as pancreatic atrophy, pancreatic lipomatosis and evidence of chronic pancreatitis such as pancreatic ductal disruptions, parenchymal calcifications[106,107] (Figure 1A-D). In young children, the CT or MRCP testing may require deep sedation or anesthesia. Also, the availability and interpretation of s-MRCP is limited to academic centers. In addition to anatomic details, endoscopic ultrasound (EUS) is also helpful in procuring biopsy in cases when a tissue diagnosis is needed. The availability of EUS with advanced endoscopist is also limited to select pediatric academic centers.

## Management of EPI

PERT is the mainstay of EPI treatment along with fat-soluble vitamin supplementation. Dosage recommendations of PERT in children are predominantly inherited from expert recommendations of CF management. Both European and North American CF guidelines outlined PERT dosage for different age groups.[96,108–111]

Currently, the PERT dose is based on age and quantity/quality of food intake. Another way to dose is based on the fat content of the food.[96,108] PERT doses are calculated either based on body weight or on the amount of fat ingested. Calculation of PERT based on fat intake is considered more physiological, accurate, and superior but cumbersome and difficult for some patients and families.[112] In infants, 2000–4000 lipase units/120 mL of infant formula (about 1600

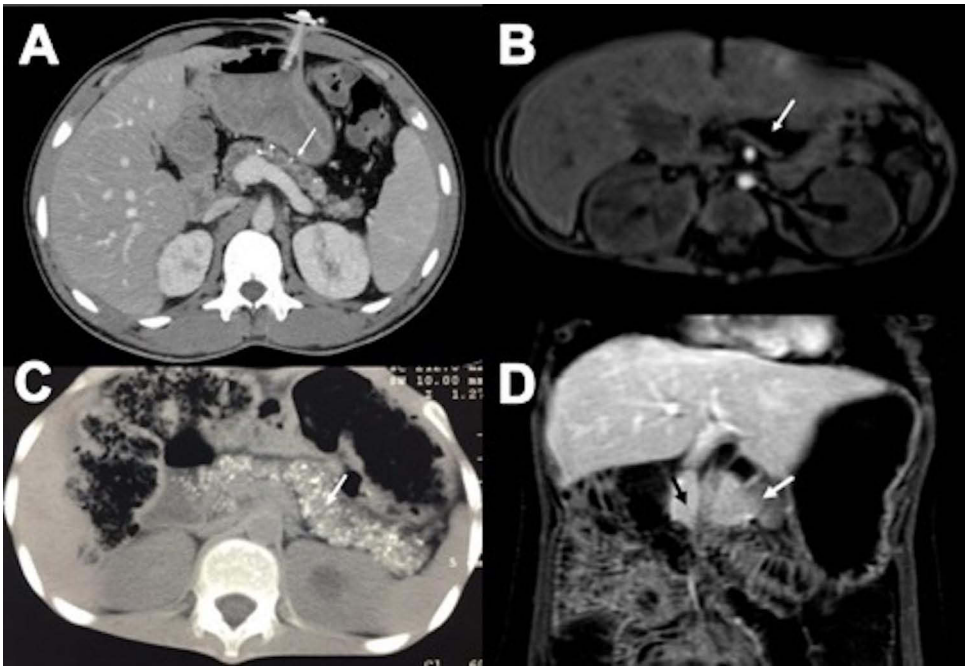


**Figure 1** (**A**) Computed tomography (axial view) of a 8-year-old patient with cystic fibrosis showing pancreatic atrophy and pancreatic calcifications (white arrow). (**B**) Magnetic resonance cholangiopancreatography (axial view) of an infant with exocrine pancreatic insufficiency from Pearson syndrome showing pancreatic atrophy with fatty replacement (white arrow). (**C**) Computed tomography (axial view) of a 5-year-old patient with exocrine pancreatic insufficiency from tropical calcific pancreatitis showing extensive pancreatic calcifications (white arrow). (**D**) Magnetic resonance enterography (coronal view) of a 4-year-old patient with exocrine pancreatic insufficiency showing annular pancreas (white arrow) and pancreatic hypoplasia with small body and tail of the pancreas (black arrow).

lipase units/gram of fat ingested per day) or per breastfeeding is recommended with a maximum daily dose of 10,000 lipase units/day.[96,108–111] For children 1–4 years of age, a starting dose of 1000 lipase units/kg for meals and 500 lipase units/kg for snacks is recommended.[96,108] Similarly, for children >4 years of age, recommended starting dose is 500 lipase units/kg/meal and 250 lipase units/kg per snack with a dose of 1000–2500 lipase units/kg/meal or 2000–4000 lipase units/gram of dietary fat with a daily maximum 10,000 lipase units/kg/day.[96,108]

A lower effective dose can be started and slowly increased for response with a daily dose not exceeding the daily maximum 10,000 lipase units/kg/day or 2500 lipase units/kg/meal.[96,108] This maximum dosage of PERT in CF evolved in the 1990s in both the US and Europe as a result of the development of a complication known as fibrosing colonopathy in CF.[110,113,114] The median dose consumed by children who developed fibrosing colonopathy was 13,393 USP lipase units/kg/day.[110,113,114] In the 1990s, PERT were often over-filled and dosage higher than 6000 lipase/kg/meal was thought to be the contributing factor for fibrosing colonopathy.[109,115] With the current daily recommendation of maximum dosage of PERT, the cases of fibrosing colonopathy were no longer being reported.[116]

There is little evidence-based literature on how to provide PERT via the enteral feeding tube.[117,118] If patients can take PERT orally, experts recommend administration of PERT at the beginning of bolus feeds (or any feeds lasting less than 3 hours duration).[118] For feeds lasting longer than 3 hours, the estimated PERT dose, based on the fat content of the enteral feeding, can be divided and given every 3 hours.[118] For continuous night time feeds, a conventional practice is to provide PERT capsules 50% orally at the beginning and the remaining 50% at the end of nocturnal enteral feedings.[118,119]

Relizorb™ (immobilized lipase cartridge) was approved by the FDA for adults with EPI in 2015, for children over five years of life in 2017, and recently got approved for use in children 2 and older. This cartridge connects in-line with enteral tube feedings and provides continuous fat absorption through the course of night-time tube feedings. Studies have shown increased omega-3 fatty acid levels and decreased subjective symptoms of malabsorption.[120,121] One cartridge is recommended for 500 mL of feeds with a maximum of two in-line cartridges.[120,121]

The Cystic Fibrosis Foundation (CFF) does not recommend using generic, non-proprietary PERT.[96] Similarly, CFF recommends against using over the counter PERT as they are not tested for efficacy or safety.[96] Registered dietitian is an indispensable member of the EPI care team and provides general guidance regarding enzyme adjustments based on the

fat content of foods and beverages. In patients with non-CF EPI, a lower range of the above mentioned doses are generally enough to successfully manage symptoms of EPI and achieve optimal nutritional status.

CF (EPI)-specific fat-soluble vitamins are recommended for patients with EPI.[122] Serum levels of fat-soluble vitamins should be evaluated at diagnosis, monitored approximately 3–6 months after initiating fat-soluble vitamin supplementation (or after dose modification), and thereafter every year.[32,96] The doses of PERT and fat-soluble vitamins should be regularly monitored by a dietitian with EPI expertise and doses should be adjusted to prevent deficiencies. Adjustment of dose of additional fat-soluble vitamin supplementation is warranted based on the levels.[32,96]

## Specific Challenges of PERT Administration in Children

Treatment with PERT poses unique challenges in infants and young children. For infants and young children who are unable to swallow capsules, encapsulated microbead or microsphere PERT formulations can be used. The enzymes are administered by opening the capsules and sprinkling the contents onto soft food mixtures with a pH of 4.5 or less (*eg*, applesauce, banana, sweet potatoes, or pureed apricot) and fed via a small spoon before each feeding.[13] PERT microbeads should not be mixed with food with a pH >7 (eg, milk) for a prolonged period of time as their enteric coating will dissolve, exposing the enzymes which will be inactivated by the exposure to gastric acid.[13] The beads should not be chewed or crushed. Acid suppression medications (H2 receptor antagonists or proton pump inhibitors) can be used to enhance the efficacy.[13] To prevent oral mucosal ulceration from the digestive enzymes, parents are advised to ensure that no beads remain in the baby's mouth after feeding by sweeping the mouth after PERT administration. In breastfed babies, enzymes left on the breast may also cause ulcerations. Also, infants can develop perianal irritation from faster transit of pancreatic enzymes and use a barrier cream to prevent this complication.

However, in infants, the maximum daily dose may be transiently exceeded. The data from the CFF registry revealed that the mean dosage per feeding in infants was approximately 1500 lipase units/kg/feed (range 641–3653 lipase units/kg/feed), and as most infants are fed every 2–3 hours, the total daily maximum was easily surpassed at least for a short period with no further documented increase in fibrosing colonopathy cases.[110]

Poor weight gain and persistence of other subjective EPI symptoms can be encountered despite adequate PERT dosage.[112] As children are growing, frequent assessments of dosing adjustments should be done based on their weight gain. Also, assessment of adherence and administration technique is recommended before dosing changes. PERT administration in children may pose unique challenges in the school environment.[112] PERT should be taken just before or during the meal. Many schools may recommend PERT be administered at the nurse's office before going to the cafeteria and if the time interval is long (>30 minutes), PERT may not be effective.[112] Due to decreased secretion of bicarbonate from the pancreas, gastric chyme may not be sufficiently neutralized, leading to inadequate dissolution of enteric coating and precipitation of bile acid. A trial of acid suppression or a PERT product with bicarbonate can be utilized in patients with persistent symptoms.[123,124] If the response to PERT is inadequate with continued steatorrhea with or without poor weight gain, further evaluation is required[125] (Table 4).

**Table 4** Factors to Consider for Poor Response to PERT and Persistence of EPI Symptoms

| |
|---|
| Ensure correct dosage is used (in relation to the fat content of the food or body weight) or consider increasing the PERT dose in smaller increments (daily dose not exceeding 10,000 lipase units/kg/day) |
| Evaluate efficacy of PERT (appropriate storage and checking expiry date) |
| Ensure administration just before the meal/snack and fat containing beverages |
| Evaluate for adherence to PERT |
| Evaluate for "graze" pattern throughout the day without taking PERT |
| Consider a trial of acid suppression if the symptoms do not improve with optimizing dose changes |
| Consider other causes of malabsorption such as celiac disease, small intestinal bacterial overgrowth, inflammatory bowel disease |

**Abbreviations**: EPI, exocrine pancreatic insufficiency; PERT, pancreatic enzyme replacement therapy.

# Individual Syndromes Related to EPI in Children

## Cystic Fibrosis

In CF, the pancreatic involvement starts in utero and continues into childhood.[13,18] CFTR is highly expressed in pancreatic duct epithelium and controls anion secretion into the lumen.[13,19] CFTR dysfunction impedes fluid and anion ($Cl^-$ and $HCO_3^-$) secretion, which results in acidic luminal contents with thick secretions leading to obstruction of ducts and eventual destruction of the pancreas resulting in EPI.[13,19] These viscid secretions plugging pancreatic ducts have been documented even in preterm infants. This destructive process results in an increase in the serum trypsinogen levels, which is the basis for IRT in CF newborn screening test.[19] The pathophysiology of pancreatic insufficiency in CF also occurs due to mechanisms such as inhibition of endocytosis in acinar cells, prevailing inflammatory milieu, and imbalance in membrane lipids in CF-regulated cells.[20] The defect in $HCO_3^-$ secretion in CF also results in acidic duodenal fluid. This leads to the irreversible inactivation of lipase and other pancreatic enzymes.[17] About 85% of CF patients are pancreatic insufficient.[21] Nearly two-thirds of these infants have EPI at birth and another 15–20% develop EPI by school age.[22,126,127]

Mutations (either homozygous or compound heterozygous) classified as I–III and VI are associated with EPI status, and usually, IV and V have pancreatic sufficiency status.[19,23] Pancreatic sufficient CF patients are more prone to acute pancreatitis (approximately 10–15%), and repeated episodes of pancreatitis may eventually lead to insufficiency.[128] In CF, multiple factors are implicated as causes of malnutrition, namely decreased intake (reduced appetite, nausea, abdominal pain interfering with intake), maldigestion or malabsorption, excessive energy expenditure (inflammatory catabolism), increased losses, and the *CFTR* gene defect itself.[24] The presence of CF-related liver disease and CF-related diabetes also further exacerbates malnutrition. In children, CF has more severe consequences with impairment of growth.[24]

There is a direct relationship between nutritional status and improved pulmonary function and subsequently survival.[129] In the 1960s and 1970s, low fat diets were commonly utilized to manage the symptoms of fat malabsorption which resulted in severe growth failure.[129] An elegant study by Corey et al compared children followed by Toronto and Boston CF centers revealed that Toronto children had improved growth and survival compared to children followed in Boston.[129] The prime difference between these centers is, patients in Toronto had high energy, high fat diet whereas in Boston, children were fed high energy, fat restricted diet.[129] The introduction of enteric coated enzymes in the form of microspheres in 1979 revolutionized the management of EPI.[25] The introduction of newborn screening of CF has tremendously improved the nutrition and overall status of CF children than those diagnosed later with symptoms.[130] Owing to these major interventions (early diagnosis, initiation of aggressive nutritional management and improvements in respiratory management), the median predicted survival published in 2021 was 52 years which has increased from ~28 years in the early 1990s.[21](Figure 2)

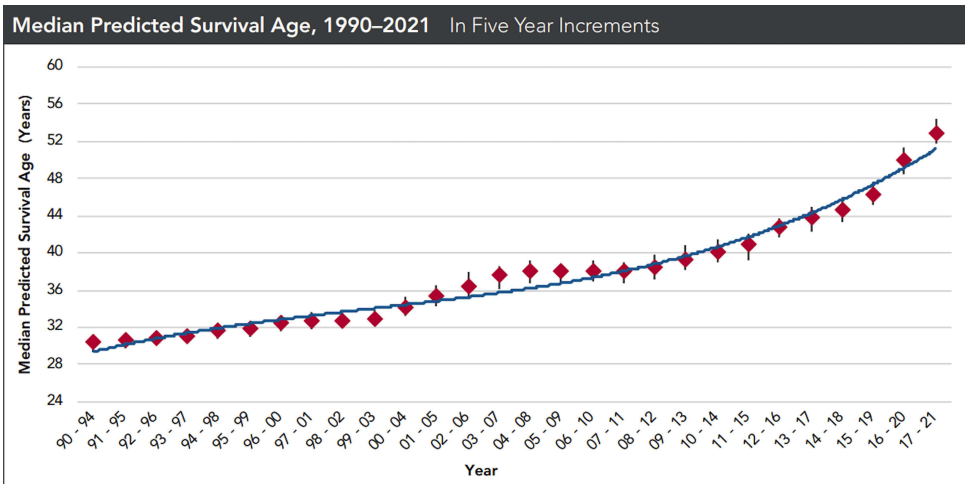


**Figure 2** Median predicted survival age of patients with cystic fibrosis from the year 1990 to 2021 in five-year increments (reproduced with permission from the Cystic Fibrosis Foundation).

**Notes**: Cystic fibrosis patients under care at CF Foundation-accredited care centers in the United States, who consented to have their data entered. Cystic Fibrosis Foundation Patient Registry, 2021 Annual Data Report, Bethesda, Maryland, ©2022 Cystic Fibrosis Foundation.

PERT, along with high fat diet and CF (EPI)-specific vitamins is the mainstay of nutritional management of CF. The Cystic Fibrosis Foundation (CFF) recommends PERT for all infants with two CFTR mutations associated with PI and in infants with stool elastase <200 μg/gm of stool or coefficient of fat absorption (CFA) <85% (in infants <6 months of age), or infants with unequivocal manifestations of malabsorption.[96] In pancreatic sufficient CF patients with recurrent episodes of pancreatitis, stool elastase testing is recommended to screen for EPI.[108]

For infants and children who are not gaining weight, feeding difficulties due to oral aversion should be evaluated. Oral aversion could be due to immature oral skills or behavioral feeding refusal. In a study involving children with CF and EPI, the behavioral and aggressive nutrition intervention improved energy intake and height for age *Z* score, but not weight for age *Z* score in preschoolers 2–6 years of age.[131] Failure to thrive in CF infants needs additional evaluation for salt deficiency, essential fatty acid deficiency, and zinc deficiency. Short term zinc supplementation (1 mg elemental zinc/kg/day in divided doses) can be provided empirically in infants who have difficulty gaining weight.[96] Hyponatremic dehydration can occur in infants and children with CF due to increased losses of salt in sweat, and low salt content of commercial baby foods.[96,132] Salt supplementation is recommended to prevent deficiency; 1/8th teaspoon of table salt (~2.5 mEq) per day for less than 6 months of age, increasing to 1/4th teaspoon of table salt per day for greater than 6 months of age.[96] In adults with CF, the BMI targets for men is 23 kg/M$^2$ for men and greater than 22 kg/M$^2$ for women. In children, due to their active growth, age and gender-specific anthropometric percentiles are used. For infants and children less than two years, the target anthropometric measures include weight for length greater/equal to 50th percentile and for children 2–18 years, BMI > or equal to 50th percentile for healthy controls of same age and gender.[108,125] Specific pediatric CF guidelines include glucose tolerance testing around 10 years of age to screen for CFRD and also, bone mineral density screening recommended at 8–10 years of age.[108]

The European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the European Cystic Fibrosis Society (ECFS) guidelines and the CFF guidelines recommend providing 110–200% of energy requirements in patients with CF to maintain nutritional status with the targeted anthropometric measurements.[108] A variety of high-calorie oral supplements are available on the market which are often recommended for CF patients who are having trouble achieving weight gain targets. Supplemental gastrostomy tube feeds (as a nocturnal infusion) are often recommended in children when oral intake is not adequate to provide the needed calories.[120,121] About 10–15% of CF patients in the US require tube feeding.[21,120]

Ivacaftor, a small-molecule potentiator of CFTR utilized in gating mutations, has been shown to improve pancreatic function in some patients.[133–137] Patients 2 years and older with at least one mutation of F508del are now eligible for the triple combination elexacaftor-tezacaftor-ivacaftor, and their efficacy on pancreatic function in early years of life remains elusive.[138,139]

## Shwachman-Diamond Syndrome

SDS is characterized by EPI, bone marrow failure, and a predisposition towards myelodysplasia or acute leukemia (mainly acute myeloid leukemia).[33–36] Most patients with SDS present in infancy with EPI symptoms or with recurrent infections.[37] The presentation is variable with nearly half of the patients present with steatorrhea and neutropenia.[33,36] Neutropenia is the most common hematological abnormality.[33] A positive family history, hypocellular marrow, and other congenital anomalies are often noted.[33–35]

Pancreatic insufficiency is due to a decrease in pancreatic acinar cell mass and symptoms are present in 90% of patients during infancy.[35–37,140] Here, the pancreatic ductal architecture and islets are unaffected and pancreatic acini are replaced by fat.[38] Similarly, the islet cells are unaffected. Radiological tests such as ultrasound, CT, or MRCP could reveal pancreatic lipomatosis.[44]

Given the rarity, most management guidelines are a result of expert consensus opinion.[36] Prior to the advent of genetic analysis, the diagnosis of SDS was essentially based on bone marrow and pancreatic abnormalities. Dror and colleagues outlined the current diagnostic criteria which incorporates biallelic *SBDS* gene mutations along with hematological findings (neutropenia which may be cyclic or chronic, anemia, thrombocytopenia, hypocellular bone marrow), pancreatic insufficiency (reduced trypsinogen in children <3 years of age and reduced isoamylase >3 years of age), and pancreatic lipomatosis on imaging, reduced stool elastase or elevated fecal fat excretion based on CFA).[32,37]

Skeletal abnormalities include short stature with or without metaphyseal dysplasia, and rib cage abnormalities.[36,37,141] Hepatomegaly and elevated liver enzymes are noted in many patients.[32,39] Other findings such as skeletal anomalies such as neurocognitive problems, height <3rd percentile, and first-degree family member with SDS.[32] Recurrent infections such as pneumonia, otitis media, bone infections, and sepsis are frequently noted. Nearly half the patients may present with failure to thrive.[39]

Management by a multidisciplinary team is recommended, and the essential members of the team include hemato-oncologist, gastroenterologist, dietician, geneticist, endocrinologist, orthopedic specialist, physical and occupational therapist, social worker, and pharmacist. Many SDS patients have an age-related improvement in pancreatic impairment over time and beyond four years, nearly 50% will stop requiring PERT.[35–37] Neutropenia rarely assumes clinical significance and responds well to low doses of granulocyte colony stimulating factor (G-CSF). Many SDS patients have responded excellently to stem cell transplantation.

## Johanson-Blizzard Syndrome

Most patients exhibit characteristic phenotypical features such as alae nasi hypoplasia or aplasia, scalp defects (cutis aplasia), hearing impairment, dental anomalies, microcephaly, cardiac anomalies, hypothyroidism, imperforate anus, and urogenital defects along with EPI.[45–49] Most patients have severe growth and developmental delay.[45–47] Similar to SDS, patients with Johanson-Blizzard syndrome have a primary failure of pancreatic acinar development and are replaced by fat and connective tissue.[16,50,51] Unlike CF, the pancreatic ductular secretion of anions and fluids is unaffected.[51] If pancreatic insufficiency is not aggressively treated, infants may succumb to malnutrition and overwhelming infections.[46]

## Pearson-Marrow Pancreas Syndrome

EPI is noted in half the patients and unlike, SDS the pancreas is fibrotic.[53] The exact pathogenesis for EPI is unclear.[54] The pancreas is normal in-utero and pancreatic damage occurs postnatally. Due to defects in oxidative phosphorylation, mitochondrial energy production is impaired which may render the pancreas prone to damage by reactive oxygen species.[16] Patients with this disorder have poor prognosis and the majority of deaths are secondary to multi-organ failure, metabolic acidosis, and severe infections.[55] Kearns-Sayre syndrome is a similar but milder phenotype predominantly involving muscles with progressive dysfunction.[16,56]

## Jeune Syndrome

Jeune syndrome or asphyxiating thoracic dystrophy was first described in 1955.[59] It is a rare autosomal recessive disorder with a global incidence estimated at 1:100,000 to 1:130,000 live births. The disease phenotype is variable. It is characterized by musculoskeletal abnormalities including a small, narrow chest leading to respiratory distress and, short-limbed dwarfism.[60] EPI is due to pancreatic fibrosis.[61,62] Renal abnormalities (cystic dysplasia/nephronophthisis), hepatic and pancreatic fibrosis, and ocular complications may occur later in life.[16,60]

## Isolated Enzymes Deficiencies

Isolated deficiencies of lipase, colipase, trypsinogen, and enterokinase have been described.[75] Enterokinase is found on the intestinal brush border and is responsible for the activation of trypsinogen and chymotrypsinogen and hence its deficiency could lead to protein malabsorption. The deficiency of trypsinogen or enterokinase is characterized by failure to thrive, hypoalbuminemia, and edema. Isolated amylase deficiency is usually due to a maturational defect in young children and resolves by 2–3 years of age and does not produce clinical symptoms as the functional capacity of salivary amylase is enough to compensate well to prevent symptoms.[142]

## Pancreatic Agenesis

Genes causing pancreatic agenesis are rare and described in Table 2. Patients with partial agenesis or hypoplasia remain asymptomatic given the high pancreatic functional reserve.[51]

## Chronic Pancreatitis Leading to EPI

In adults, most patients have CP secondary to alcoholism and biliary tract diseases. In children and adolescents, majority of CP are associated with genetic abnormalities (mutations such as *PRSS1, CFTR, SPINK1*, and *CTRC*), biliary obstruction (eg, pancreas divisum, sphincter of Oddi dysfunction, gallstones), and drug toxicity or side-effects[12,143] (Table 1). In a multi-center evaluation by the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) consortium, 26–30% of children with acute recurrent pancreatitis or CP were found to have EPI which is similar to adults (33%).[143–145] Alcohol and tobacco were noted in about 50% of adults as risk factors, whereas in children, alcohol and tobacco consumption were associated with 1% and 7% respectively.[143] In the study by Schwarzenberg and colleagues, 18% of patients developed EPI within six years of their first episode of acute pancreatitis.[143] Tropical chronic pancreatitis is a rare condition noted in south India, Sri Lanka, and other tropical countries in which children often have recurrent episodes of pancreatitis, which leads to pancreatic insufficiency.[146] The exact etiology is unclear, but malnutrition, nutrient deficiencies, dietary cyanogen toxicity, and an underlying genetic predisposition have been proposed.[146]

In another INSPPIRE study, within six years of the initial acute pancreatitis episode, the cumulative proportion with EPI was noted as 18% (95% CI: 12.4–25.6%).[147] EPI patients may present clinically with manifestations of malabsorption or can be subclinical.[92] Many experts recommend PERT if fecal elastase is <100 µg/g or 72-hour fecal fat (coefficient of fat absorption >15% in infants less than six months and >7% for patients greater than 6 months).[145,148] PERT dosages in CP management in children are adopted from CF guidelines.[148] For children younger than four years, 1000 lipase units/kg/meal and for children older than four years, 1000–2500 lipase units/kg/meal.[148] For snacks, half the PERT dose is recommended.[148] Similar to CF management guidelines, the daily maximum dose of <10,000 lipase units/kg is recommended to prevent fibrosing colonopathy.[114]

## Conclusions

Despite many similarities, etiological conditions causing EPI in children are unique from adults and specific challenges exist in the management of EPI in children. Clinicians should have a high index of suspicion for early diagnosis and aggressive management to optimize the clinical outcome. Children with EPI should be evaluated frequently for nutritional assessments. The literature regarding the management of EPI in children is based on experience gained from CF management, and evidence-based management of pther causes of EPI in children is limited. Pancreatic enzyme replacement therapy (PERT) is the cornerstone of EPI treatment along with fat-soluble vitamin supplementation. PERT can either be dosed based on the age and diet or more accurately based on the fat content of the food, (2000–4000 lipase units/gram fat). The PERT dosage can be slowly titrated for response with a daily dose not exceeding 10,000 lipase units/kg/day or 2500 lipase units/kg/meal. Multidisciplinary intervention is the key to successful management and favorable outcomes.

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