Section A -Research paper

Pancreatic affection in Children Diagnosed with Cystic Fibrosis

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Abstract:

Background: Cystic fibrosis (CF) is the leading etiology for exocrine pancreatic insufficiency (EPI) in children, followed by chronic pancreatitis, and other genetic disorders. Pancreatitis has historically been considered rare in CF due to pancreatic parenchymal loss early in infant development. However, newborn screening, advancements in genetics, and CF Transmembrane Conductance Regulator (CFTR) modulator therapies have all increased the proportion of CF patients with pancreatitis. Newborn screening helps to identify CF patients even before symptoms may manifest. The cystic fibrosis transmembrane conductance regulator gene, which encodes a chloride and bicarbonate channel expressed in the apical membrane of epithelial cells. The gene is expressed in multiple organ systems, which explains the wide variety of medical conditions experienced by people with CF, affecting the pulmonary, endocrine, gastrointestinal, pancreatic, biliary and reproductive systems.

Conclusion: Pancreatic insufficiency common in children with cystic fibrosis so early diagnosis and important management improve outcome of patients regarding gaining weight and decrease pulmonary exacerbation as result decrease mortality. recommend to cases with positive in prenatal screaning and pancreatic sufficient to follow up.

Key words: Cystic Fibrosis, Exocrine pancreatic insufficiency, Pancreatic function test, CFTR

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Introduction

Cystic fibrosis (CF) is one of the most common autosomal recessive genetic disorders in the United States and the most common among Caucasians of European descent. The disease is caused by mutations in CFTR, the cystic fibrosis transmembrane conductance regulator gene, which encodes a chloride and bicarbonate channel expressed in the apical membrane of epithelial cells. The gene is expressed in multiple organ systems, which explains the wide variety of medical conditions experienced by

people with CF, affecting the pulmonary, endocrine, gastrointestinal, pancreatic, biliary and reproductive systems**(1).** Generally, mutations (such as the most common, F508del) that cause the most severe disruption of CFTR function are associated with worse clinical outcomes. Because heterozygotes carry only one CFTR mutation, they express half as many CFTR channels as people without a CFTR mutation **(2).**

EPI is one of most well-known complications of CF, with CF being the most common cause for EPI in children. Greater than 85% of CF patients in the CF Foundation registry are noted to be EPI in children, as defined by use of PERT. While fecal elastase-1 (FE-1) testing is the most commonly used diagnostic test to identify EPI **(3).**

Monitoring of exocrine pancreatic function in children using indirect and direct tests has recently been reviewed by the Pancreas Committee of the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) in discussing endoscopic pancreatic function testing (ePFT). Beyond the stool, breath, and endoscopic tests discussed, new data has emerged examining exocrine pancreatic function in CF patients using ultrasound (US) **(4)** and magnetic resonance imaging (MRI) **(5).**

Cystic fibrosis (CF) is always associated with some degree of pancreatic damage. Approximately 75% of infants with new diagnosis of CF have EPI. The type of CFTR mutation determines the risk of pancreatitis and of EPI in CF patients. Some 85% of infants with biallelic severe (classes I, II, III, VI) CFTR mutations have moderate PEI within 3–4 months of age, whereas heterozygote severe or homozygote mild mutation may develop PEI during life course **(6).**

Pancreatic insufficiency is treated with pancreatic enzyme replacement as well as nutritional support with high-calorie fat diet, vitamin supplementation and sodium chloride supplementation. Intestinal blockage prevention and treatment requires oral hydration, osmotic laxatives and hyperosmolar contrast enemas as needed **(7).**

Cystic fibrosis

Cystic fibrosis (CF), a monogenic disease transmitted in an autosomal recessive pattern, is multisystemic and chronic and originates as a consequence of pathogenic changes in the CFTR gene located on the long arm of chromosome 7 (locus 7q.31) that encodes for the protein known as the CF transmembrane conductance regulator (CFTR) **(8).**

Genetics

Characteristics of the Human Cystic Fibrosis Gene and Encoded CFTR Protein

The structure of normal CFTR protein comprises 2 groups of 6 membrane-spanning structural motifs, 2 intracellular nucleotide-binding folds (NBFs), and a highly charged "R domain," including several phosphorylation sites. Phosphokinase A-mediated phosphorylation of the R domain and sustained adenosine triphosphate (ATP) levels within the NBFs are required for chloride channel activation. The CFTR gene is located on the long arm of chromosome 7. CFTR helps to transport chloride and bicarbonate across secretory epithelia, regulating salt and water secretion and absorption as well as epithelial surface hydration **(9).**

CFTR mutations disrupt the expression, function, and stability of messenger RNA (mRNA) and CFTR protein, interfering with fluid and electrolyte homeostasis. One of the main signs of CF is an aberrant excessive release of salt from the sweat

glands that is not reabsorbed by the sweat duct cells. The gold standard for diagnosing CF is measurement of the chloride excreted in sweat **(10).**

Genetic mutation types in CFTR

Mutations of the CFTR gene fall into six different classes that roughly correspond to specific types of CFTR dysfunction. In general, mutations in classes I to III cause more severe disease than those in classes IV to VI. However, clinical manifestations of CF caused by any particular combination of mutations can vary, perhaps due to effects of gene modifiers **(11).**

Clinical features of cystic fibrosis

Neonates may present with meconium ileus. Smaller children may present with pulmonary complications such as recurrent pneumonia, upper respiratory infections, wheezing, and coughing. Gastrointestinal manifestations include failure to thrive with malabsorptive stools, recurrent abdominal pain **(12)**.

Common symptoms and signs of pancreatic insufficiency include steatorrhea, characterized by frequent, bulky, foul-smelling stools that may be oily, as well as failure to thrive or poor weight gain resulting from malabsorption of fat and protein. Moreover, patients with exocrine pancreatic insufficiency often develop dysfunction of the endocrine pancreas, leading to glucose intolerance and CF-related diabetes **(13).**

Diagnosis of cystic fibrosis

Diagnostic criteria of cystic fibrosis

Patients diagnosed with classic or typical CF have at least one phenotypic CF characteristic plus a sweat chloride above 60 mmol/L. In contrast, patients with non-classic or atypical CF have phenotypic features in at least one organ and a sweat chloride value in the intermediate range (30–60 mmol/L) but proof of CFTR dysfunction via identification of 2 disease causing CFTR mutations and/or an abnormal nasal potential difference measurement (NPD) **(14).**

Sweat chloride

In children clinically suspected to have cystic fibrosis, a referral to a CF center for sweat testing is indicated. False positives are rare, but sweat chloride may elevate falsely in other pathologic syndromes and situations, including improper testing technique, atopic dermatitis, untreated adrenal insufficiency, glycogen storage disease, panhypopituitarism, hereditary nephrogenic diabetes insipidus, hypothyroidism, pancreatitis, malnutrition, mucopolysaccharidosis, ectodermal dysplasia and prostaglandin E1 infusion **(15).**

Cystic Fibrosis Diagnostic Challenges

Fecal elastase

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 **(16).**

Prenatal screening

A study has estimated that 0.8–13.3% of fetuses with Fetal Echogenic Bowel (FEB) will have CF. When both parents are carriers of pathogenic CFTR variants, there is a one-in-four chance (25%) of CF in the child, which is 625 times greater than the risk in the general population (0.04%). Prenatal CFTR testing is usually done through chorionic villus sampling or amniocentesis; however, clinical practice is currently

shifting toward noninvasive prenatal testing for CF**.** No fetus was found to have biallellic pathogenic *CFTR* variants; possibly due to the small sample size and the relatively low CF rate in pregnancies with FEB (2–13%). The second study tested 25 fetal samples in pregnancies with detected FEB. One pathogenic variant was detected (CF carrier) and no CF diagnoses occurred before or after birth **(17).**

Genetic mutation analysis

The CF gene mutation panel detects the common mutations in the cystic fibrosis. In a CF gene mutation panel, the laboratory specifically examines the CFTR gene on each chromosome 7 for the 23 mutations. If the initial panel of mutations demonstrates a single mutation, additional testing for other less common mutations may be indicated if the individual is suspected of having CF. The CF mutation panel can be used as part of prenatal testing to determine whether prospective parents are carriers of a CF gene mutation and therefore at risk of passing the gene mutation to future children **(18).**

Importance of analyzing cystic fibrosis phenotype

People with CF commonly suffer from chronic bronchitis, bronchiectasis, chronic sinusitis, gastroesophageal reflux disease, constipation, diarrhea, diabetes, chronic pancreatitis, malnutrition, delayed development, male infertility, osteoporosis, asthma, and nasal polyposis. All of these conditions contribute to the morbidity associated with CF, but a substantial proportion of CF morbidity is associated with chronic and recurrent respiratory infections. Interestingly, patients with CF are not equally susceptible to all respiratory pathogens. In particular, they are at risk for infections caused by Pseudomonas, Burkholderia, Aspergillus, and nontuberculous mycobacteria **(19).**

Treatment and management of CF

Mucolytic Medications

Dornase Alfa

Dornase alfa produces a mucolytic effect by depolymerizing DNA polymers. It produces a mild increase in FEV1(forced expiratory volume after 1 second) in patients with cystic fibrosis **(20).**

N – Acetylcysteine

N-acetylcysteine has anti-inflammatory and antioxidative properties. These agents help reduce the reactive oxygen species and inflammatory mediators that cause the insult in respiratory airways**.**

Hypertonic saline

The addition of 3% hypertonic saline on the mucus surface improved its clearance, with an even greater effect than Dornase alfa **(21).**

Antibiotic

Antimicrobial therapies are also used as either prophylaxis or chronic suppressive treatment in patients with cystic fibrosis (PwCF). The use of antibiotics (commonly azithromycin) in CF, however, is more widely accepted. Antimicrobial therapies are also used as either prophylaxis or chronic suppressive treatment in patients with cystic fibrosis (PwCF). CF alone is typically not an indication for RSV prophylaxis but may be considered with other risk factors for severe RSV pulmonary illness. The use of antibiotics (commonly azithromycin) in CF, however, is more widely accepted. Chronic azithromycin uses increases macrolide resistance in common upper respiratory

bacterial species, but this may have little impact on antibiotic selection to treat CF pulmonary exacerbations. There are data indicating that azithromycin reduces the ability of tobramycin to kill *P. aeruginosa* **(22).**

Table 1. Chronic Maintenance Therapies for Airway Infections in patients with cystic fibrosis (PwCF) **(23).**

Drug	**Route**	**Usual Dose**	**Indications**	**Approval Status**
Tobramycin	Inhalation	Solution: 300 mg BID DPI: 112 mg BID NIS: 80-160 mg BID	-*Pseudomonas aeruginosa* eradication (grade A) -Maintenance therapy in persons aged ≥6 years and *Pa*[a]	FDA, HC, EMA
Aztreonam	Inhalation	75 mg TID	-*P. aeruginosa* eradication -Maintenance therapy in persons aged ≥6 years and *Pa*[a]	FDA, HC, EMA
Colistin	Inhalation	NIS: 75 mg BID DPI: 1 662 500 IU BID	-*P. aeruginosa* eradication -Maintenance therapy in persons aged ≥6 years and *Pa*[b]	EMA
Levofloxacin	Inhalation	240 mg BID	Maintenance therapy in persons aged ≥6 years and *Pa*[b]	FDA, HC, EMA
Amikacin	Inhalation	590 mg OD	- Maintenance therapy in persons aged ≥6 years and *Pa*[b] -NTM therapy	FDA, EMA
Azithromycin	Oral	500 mg daily 3×/week	Maintenance therapy in persons aged ≥6 years with (grade B) or without *P. aeruginosa* (grade C)	FDA, HC, EMA

PwCF, persons with cystic fibrosis; DPI, dry powder inhalation; NIS, nebulized intravenous solution; FDA, Food and drug administration; HC, Health Canada; EMA, European Medicines
Agency; BID, two times a day; TID, three times a day; OD, once daily. a: Grade B recommendation for mild disease; grade A recommendation for moderate to severe disease. b: Limited evidence for alternate agents.

Pancreatic enzyme replacement therapy

Most people with cystic fibrosis (CF) (80% to 90%) need pancreatic enzyme replacement therapy (PERT) to prevent malnutrition. Enzyme preparations need to be taken whenever food is taken, and the dose needs to be adjusted according to the food consumed **(24).**

Diet supplements

Individuals with CF are encouraged to consume a high-fat diet with supplemental fat-soluble vitamins to compensate for malabsorption. Additionally, patients living with CF are encouraged to consume a high-calorie diet to maintain a healthy weight and combat chronic inflammation and frequent infections that are commonly encountered **(25).**

CFTR modulators

Types of CFTR modulators and their targeted mutations: There are different types of CFTR modulators (potentiators, correctors, amplifiers, and stabilizers) and the targeted classes of CFTR mutations.

Gene therapy

Gene therapy offers great hope for the treatment of genetic diseases/disorders. By replacing the genetic mutation with a "correct version" of the CFTR gene, this method offers a potentially permanent cure. The number of cells harboring wild-type CFTR that is needed to translate into clinical benefit in patience remains unknown. However, theoretically correcting a stem cell population within the airways may provide a renewable and long-term source of endogenous cells capable of renewing the damaged epithelia with cells that express wild-type CFTR. Yet surprisingly, with the exception of a Phase I and II clinical trial for MRT5005, a drug that delivers CFTR-encoded mRNA to the lungs (RESTORE-CF), there are no other clinical trials for CF gene therapy **(26).**

This may largely be due to several reasons: The need for repeated delivery due to the inability to target stem/progenitor cells of the airways to sustain expression during cell turnover. Suboptimal delivery or low efficiency of targeting of the donor plasmid/gene to the CF airways due to the highly inflammatory microenvironment, the inability to deliver large DNA fragments of the *CFTR* gene effectively with current delivery methods, Concerns of off-target safety that can result in insertional mutagenesis and immune barriers limiting effective delivery of viral vectors **(27).**

Pancreatic complications

Exocrine pancreatic insufficiency in CF

Impairments in both duodenal and pancreatic bicarbonate secretion, coupled with gastric acid hypersecretion in some CF patients, results in an acidic intestinal luminal pH, which may impair enzyme activity and thereby contribute to malabsorption. PERT has been well-established as an effective therapy for EPI, when dosed appropriately, in malnourished patients and/or those exhibiting signs/symptoms of malabsorption **(28).**

Exocrine Pancreatic Insufficiency Diagnosis by Imaging

Transabdominal US is the most common modality for assessing the pancreas in children given it is non-invasive, low cost, and broadly available. MRI-based assessment of exocrine pancreatic function has been of increasing interest to pancreatologists with its potential ability to provide high-fidelity cross-sectional structural information together with organ function. The most common modality to do this is secretin-magnetic resonance cholangiopancreatography (s-MRCP). In CF, s-MRCP is able to distinguish CF-PI from CF-PS and healthy controls, shows good positive correlation with FE-1 ($r = 0.84$), and has excellent diagnostic performance in predicting EPI in CF patients when using an intestinal volume of <70 mL at 13 minutes post-secretin (AUROC = 0.95, sensitivity = 100%, specificity = 77%) **(29).**

Pancreatitis in CF

Nearly a decade ago, Ooi et al. put forward a model where individuals with extreme lack of CFTR function or near-normal CFTR function are unlikely to develop pancreatitis. However, as CFTR dysfunction decreases, but is not eliminated, individuals' risk for developing pancreatitis increases. CFTR mutations have been implicated in pancreatitis pathogenesis for decades and additional recent papers have further supported this **(30).**

Endocrine – exocrine interactions in CF

Recent studies showing that endocrine and exocrine microcirculation are tightly intercalated and that insulin levels affect exocrine acinar cell stress provide new and compelling evidence that historical separation of the exocrine and endocrine pancreas is flawed. Future research needs to examine the endocrine and exocrine functions of the pancreas in parallel to better understand how loss of CFTR function may affect both nutrition and diabetes in CF **(31).**

Exocrine pancreatic insufficiency

Prevalence of EPI

A study of the prevalence of EPI in patients admitted with acute pancreatitis found in more than half (62%) of patients, reducing over follow up to 35%. The risk of EPI was doubled in severe compared to mild acute pancreatitis **(32).**

Causes of pancreatic insufficiency

Pancreatic disorder

There are several causes which include tropical pancreatitis, idiopathic pancreatitis, ductal obstruction (pancreas divisum, pseudocysts, stones, tumors, and trauma), mutations in cystic fibrosis genes, hereditary pancreatitis and systemic diseases such as systemic lupus erythematosus **(33).**

Extra Pancreatic disorder

It could result from disease activity (autoimmune changes) or secondary to medications used in the treatment. EPI has been associated with HIV infection and is considered an important cause of chronic diarrhea in patients with HIV **(34).**

Diagnosis of EPI

Indirect Pancreatic Function Tests

Pancreatic function tests are widely classified as indirect or direct tests. 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-power field) involves microscopic analysis of fecal fat.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. 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 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 **(35).**

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. 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.

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 **(36).**

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 Cholicysto kinin or secretin stimulation is performed**.** 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 **(37).**

Treatment of gastrointestinal manifestations of CF includes treatment of pancreatic insufficiency and management of CF-related diabetes as well as prevention and treatment of intestinal blockage **(7).**

CFTR modulators – targeted treatment in CF disease

In recent years targeted therapy in the form of CFTR modulators has revolutionized the treatment of patients with CF. Oral, small molecules were developed that target the CFTR protein and have proven to be clinically successful in correcting the defect of the CFTR protein in vivo **(38).**

Management of EPI

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. PERT doses are calculated either based on body weight or on the amount of fat ingested. 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**.** CF (EPI)-specific fat-soluble vitamins are recommended for patients with EPI. 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 **(37).**

Side effects

Despite PERT's vital component to any PI CF patient treatment regimen, PERT has side effects that must be considered by the clinician. Fibrosing colonopathy is a well-known complication of PERT associated with high PERT doses **(24).**

Fat-soluble vitamins

And children with CP should have fat-soluble–vitamin levels measured every 6–12 months. If patients are supplemented with vitamins, levels should be monitored 3 months after dose adjustment. Fat-soluble vitamins deficiency is secondary to fat malabsorption, improvement is expected with optimized PERT supplement. Fat-soluble vitamins should be supplemented for deficiencies accordingly **(39).**

Vitamin A

The predominant circulating vitamin A is in the form of retinol. Serum retinol levels are not useful in assessing vitamin A body stores. Serum retinol is physiologically well controlled and kept at a homeostatic range. Thus, its level is not correlated with vitamin A deficiency and may not correlate in response to vitamin A supplementation. The serum retinol is useful when measured in a population and provides valuable information on the vitamin A status of a population **(5).**

Table 2. Fat soluble vitamins supplement **(39).**

Vitamins	**Dosage**
Vitamin A	
Birth to 6 months	400 mcg of (RAE)
Infants between 7 and 12 months	500 mcg RAE
1–3 years	300 mcg RAE
4–8 years	400 mcg
9–13 years	600 mcg RAE
Boys at 14–18 years	900 mcg
Girls at14–18 years	700 mcg RAE
Vitamin D	
Infants	400–500 IU daily
1–10 years	800–1,000 IU daily
>10 years	800–2,000 IU daily
Vitamin D deficiency without hypoglycemia	Vitamin D ranging from 25 to 125 mcg (1,000–10,000 IU) per day should be provided for 8–12 weeks to quickly correct the deficiency, then continue 10–25 mcg (400–1,000 IU) per day as maintenance.
Vitamin D Deficiency with hypocalcemia	Additional 30–75 mg/kg/day of elemental calcium
Vitamin E	
Infants	40–50 IU
toddlers	80–150 IU
4–8 years	100–200 IU
>8 years	200–400 IU
Vitamin E Deficiency	start at 10–25 IU/kg/day and may be increased by small increments (25–50 IU/kg/day every 3–4 weeks) to a maximum of 100–200 IU/kg/day, best offered as a single morning dose
Vitamin K (with prolonged INR)	

Vitamins	Dosage
	2.5–5 mg oral or 1–2 mg I.M., I.V., subcutaneous

RAE: Retinol activity equivalents, IU: International Units, INR: International normalized ratio

Vitamin D

In children, 20 ng/ml for 25(OH)-D levels is still considered sufficiency, however, a higher cutoff of 32–100 ng/ml is suggested in adults. The US Cystic Fibrosis Foundation recommends levels >30 ng.

Vitamin E

Alpha and gamma tocopherol levels are monitored in laboratory. Alpha Vitamin E reflects vitamin E mainly from supplement and gamma Vitamin E from food intake primarily from plant **(40).**

Vitamin K

Serum vitamin K level is not very useful in reflecting the deficiency status, as it only indicates the vitamin K intake over past 24 h. Protein induced by vitamin K absence or antagonism (PIVKA) and des-gamma-carboxy-prothrombin (PIVKA-II) are functionally defective coagulation factors in vitamin K deficiency status. Phylloquinone is the main dietary form of vitamin K coming primarily from green leafy vegetables **(41).**

Other nutrients

Water-soluble vitamins, trace elements and minerals (39).

Research data in studying water-soluble vitamin deficiencies in pediatric patients with EPI is limited. Vitamin C and vitamin B12 level could be low in adult patients with CP**.**

Essential fatty acid

Essential fatty acid deficiency (EFAD) can be observed in patients with CF. Essential fatty acids include polyunsaturated fatty acids which can be metabolized to alpha-linolenic acid (n-3) and linoleic (n-6). N-3 fatty acid is metabolized to docosohexaenoic acid (DHA) and N-6 fatty acid is metabolized to arachidonic acid (AA). The benefits of supplementation of antioxidants or DHA were observed in some studies; however, they were not consistent to recommend routine supplements yet **(42).**

Role of Enteral Tube Feeding

Enteral tube feedings include both short-term administration (usually <3 months) using nasogastric or nasojejunal tubes and long-term administration with gastrostomies, gastrojejunal tubes, or jejunal tubes. Current recommendations for tube feeding in CF patients include administration of 30%–65% of their total estimated calorie needs as a nocturnal infusion. This practice allows patients to receive supplemental calories in addition to their daytime oral diet. About 10%–12% of CF patients need supplemental tube feedings **(43).**

Conclusion

Pancreatic insufficiency is common in children with cystic fibrosis. So, early diagnosis and good management improve the outcome of patients regarding gaining weight and decrease pulmonary exacerbation and consequently decrease mortality. Follow up is recommended for positive cases in prenatal screening to avoid sudden pancreatic insufficiency.

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