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DIGESTIVE OUTCOMES IN CYSTIC FIBROSIS

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ABSTRACT

Cystic fibrosis (CF) is the most frequent life-limiting autosomal recessive disease in Caucasians, affecting the respiratory tract, but also the pancreas, gut, and hepatobiliary tract. CF is caused by variants in the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) gene. Prognosis of CF has markedly improved over the last 20 years because of the management in CF centers and recent introduction of CFTR modulators, aimed at correcting the defective CFTR protein. There are nowadays more CF adults than children, with a predicted median survival age of around 50 years in high-income countries. Around 85% of CF patients have pancreatic insufficiency present at birth. Gastroesophageal reflux disease (GERD) is more frequent in CF patients, but its role on decline in lung health is controversial. Distal small bowel obstruction syndrome (DIOS) caused by meconium-like stool plugs occurs at any age after the neonatal period, affecting up to 15-20% of CF patients. Because of increased life expectancy, most CF patients are expected to live to their fifties or beyond, when cancer is more frequent. In addition, CF is associated with a higher risk for GI malignancy as compared with the general population. Colorectal cancer represents the most significant risk, and colonoscopy-based screening is recommended from 40 years of age onwards. Other digestive outcomes in CF reviewed in this paper include meconium ileus, *Clostridium difficile* infection, intussusception, acute appendicitis, small intestinal bacterial overgrowth, appendiceal mucocele and rectal prolapse. Every CF Center should comprise a gastroenterologist with expertise in the care of CF patients.

Keywords:

Cystic fibrosis pancreatic insufficiency distal intestinal obstruction syndrome colorectal cancer CFTR modulators acute recurrent pancreatitis

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive, multisystemic disorder affecting the respiratory tract, pancreas, gut, hepatobiliary tract, and male reproductive tract. CF is caused by mutations (variants) in the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) gene, which is located on chromosome band 7q31.2 (1). CF is the most frequent life-limiting inherited disease in Caucasians, with an incidence ranging between 1/3,000 and 1/6,000 live births in populations of European descents. CF is much less common in African and Asian populations, with an incidence of around 1/17,000 and 1/32,000, respectively. Although CF remains a serious disease with a heavy burden on patients and families, recent therapeutic advances have dramatically changed the prognosis of the disease.

The discovery of the CFTR gene in 1989 allowed the identification of the structure and function of the CFTR protein, which is a chloride channel transporting chloride and bicarbonate (2). The CF phenotype depends on the type of variants in the CFTR gene, which result in CFTR protein deficiency or dysfunction, thereby disrupting the transport of sodium and chloride ions across epithelial and other cell membranes. The CFTR protein is expressed in epithelial cells of lungs, pancreas, liver, intestines and sweat glands. The CFTR gene consists of 27 exons and the CFTR protein contains 1480 amino acids (3). As a result of the CFTR protein deficiency or dysfunction, fluid transport is abnormal, and mucous secretions become dehydrated and thickened, ultimately impairing organ function. In the lungs, thickened mucus adheres to

airway surfaces, which leads to decreased muco-ciliary clearance, and increased risk for inflammation and infection. In the pancreas, thickened secretions obstruct intra-pancreatic ducts, reducing delivery of digestive enzymes to the intestines and impairing digestion of key nutrients.

More than 2,000 variants of the CFTR gene have been reported (3). Variants have been categorized into 6 classes depending on their effects on CFTR protein structure, expression, and function (Figure 1):

- Class I variants lead to defective protein synthesis and absence of functional CFTR at the epithelial cell surface;
- Class II variants lead to defective CFTR protein processing and maturation, and to absence of functional CFTR at the epithelial cell surface. F508del (now called p.Phe508del), the most frequent CF variant worldwide, belongs to this class; p.Phe508del stands for the codon deletion in exon 10 for phenylalanine at position 508 in the CFTR protein. The variant p.Phe508del represents up to 90% of CF-causing alleles in Denmark and 25% in Turkey, with a clear northwest to southeast gradient in Europe;
- Class III variants lead to defective channel regulation or "gating". The CFTR protein is present at the apical membrane, but is not functional;
- Class IV variants lead to the presence at the apical membrane of a CFTR protein with reduced anion conductance;
- Class V variants lead to abnormal splicing resulting in a reduced amount of normal CFTR protein;
- Class VI variants lead to a CFTR protein with defective stability and absence or severe reduction of CFTR at the epithelial cell surface.

Class I, II, and III variants are associated with little or no CFTR function and linked to a severe phenotype, including pancreatic insufficiency and recurrent pulmonary exacerbations. Class IV, V, and VI variants are associated with residual CFTR function and linked to a mild phenotype, including pancreatic sufficiency early in life and few and/or mild pulmonary exacerbations. However, it is difficult for a given patient with CF to predict the phenotype from the genotype. Other factors play a role in the severity of CF, *e.g*. gene modifiers, epigenetic and environmental factors (tobacco, pollution, socio-economic status and compliance to treatment) (2).

Due to therapeutic advances and multidisciplinary health care coordinated and delivered by specialized centers, prognosis of CF has markedly improved over the last 20 years. In high-income countries, there are nowadays more adults with CF than children, meaning that CF has become an adult disease. The US CF Foundation reported a predicted median survival age (the age at which 50% of currently born patients with CF are expected to survive if mortality conditions remain similar) of 48.4 years in 2019. Registry data show a predicted median survival age ranging from 44.4 (Ireland) to 52.1 years (Canada). It means that half of the infants born today with CF may expect to survive into their fifth decade (2). The number of pregnancies and paternities among patients with CF has substantially increased over the last two decades, as well as the rate of employability (4,5). Median age at death ranges from 29 to 36 years (6). Pulmonary bronchiectasis and chronic lung infection and inflammation leading to respiratory failure remains the main cause of morbidity and mortality. Increased survival and the involvement of gastrointestinal (GI) and hepatobiliary tracts require the need for more extensive knowledge of CF among gastroenterologists.

The aim of the present paper is to review narratively the digestive outcomes of CF with a special emphasis on the role of gastroenterologists in their management and follow-up. Most GI manifestations of CF present with abdominal pain (7) and their pathophysiology remains often obscure, involving mainly dysmotility, dysbiosis, and inflammation (8). Perspectives for patients with CF related to emergent therapies aiming at correcting CFTR dysfunction will also be highlighted. Liver and biliary disease is out of the scope of this review.

NEWBORN SCREENING

Attempts to screen neonates for CF started in the late 1970's. Newborn screening (NBS) programs are nowadays implemented in many nations worldwide, including Australia and New Zealand, the US and Canada, and more than 20 European countries (9). Most programs have adopted a two-tier approach involving measurement of immunoreactive trypsin (IRT) and/or pancreatitis-associated protein (PAP) followed by testing for the most frequent CFTR variants if abnormal. There is strong evidence to support NBS, particularly with respect to nutritional benefits and well-being, provided that appropriate management in specialized CF centers is available. Early diagnosis may not only optimize nutritional status and quality of life but is also associated with improved pulmonary health. Children diagnosed due to symptoms rather than by newborn screening are diagnosed later (15 months of age as opposed to 4-6 weeks) and have more complications including pulmonary exacerbations and decreased lung function. NBS for CF is a cost-effective public health strategy (1).

MECONIUM ILEUS

Meconium ileus (MI) is a neonatal emergency that should be managed in a center familiar with CF and where a pediatric surgeon with expertise in MI is available. MI can be simple or complex. In simple MI, a viscid and thick meconium obstructs the terminal ileum and leads to small bowel dilatation proximal to the obstruction. Complex MI is related to complications as volvulus, necrosis, atresia, or perforation followed by the extrusion of the meconium into the peritoneal cavity, namely meconium peritonitis. MI occurs in approximately 10% of patients with CF and is commonly associated with class I-III CFTR variants. MI and meconium peritonitis are increasingly suspected *in utero* due to hyperechoic bowel and/or peritoneal calcifications on ultrasound. These abnormalities imply to propose screening for CF to parents with the assessment of their CFTR gene carrier status. If both parents are carriers of CF, genetic counseling is proposed to discuss the risks of having a child with CF and the future implications. If not identified prenatally, MI presents usually with intestinal obstruction during the first hours of life. In case of severe abdominal distension and peritoneal signs and/or circulatory failure, complex MI is very likely and surgery urgently needed (10).

Simple MI is managed conservatively *via* disimpaction with the use of hyperosmolar enemas given under low hydrostatic pressure and fluoroscopic guidance to ensure that the solution reaches the terminal ileum. The most efficient solution is the water soluble radioopaque contrast medium sodium amidotrizoate (Gastrografin®) diluted with water (11). Warm saline is infused thereafter into the rectum once or twice a day for several consecutive days to facilitate full evacuation of meconium. If hyperosmolar enema is unsuccessful, surgery is needed. The primary surgical intervention is disimpaction of the meconium by irrigating the obstructed bowel with Gastrografin® or warm saline. Bowel resection is reserved for complex

cases and depends on the extent of bowel injury. Patients with CF and MI are not different from those with no history of MI in terms of lung function and nutritional status. However, the risk of developing distal intestinal obstruction syndrome (DIOS) later in life is 3-4 times higher in patients with CF and MI than in the CF general population. CF is the main but not the only cause of MI. Since newborn screening based on IRT can be falsely normal in patients with CF and MI, all neonates presenting with MI need to undergo screening for CF. Most patients with CF and MI have pancreatic insufficiency (10).

PANCREATIC INSUFFICIENCY

Cystic fibrosis of the pancreas was first identified in 1938 by the American pathologist Dorothy Andersen as a form of lethal malabsorption distinctive from celiac disease with an abnormal pancreas on autopsy (12). The changes in the pancreas were interpreted as the result of an abnormality in the pancreatic secretion, which is precipitated as eosinophilic material in the lumina of acini and ducts. Main ducts are often patent but are sometimes plugged with secretion or are atretic. There is a progressive change with age, with increase in the contents of the lumina, and gradual atrophy of acini, replacement by fibrous tissue and fat, and cyst formation (Figures 2 and 3). Progressive destruction of the exocrine pancreas leads to pancreatic insufficiency (PI) (11,13).

PI is characterized by maldigestion of macronutrients and micronutrients - particularly fat-soluble vitamins (A, D, E, K) - as a consequence of insufficient delivery of pancreatic enzymes into the duodenum. PI occurs when postprandial enzyme output is <10% of normal. Around 85% of patients with CF have PI present at birth. PI is highly correlated with the type of variants of the CFTR gene. Patients with 2 severe CFTR variants (classes I-III) tend to have early PI, often being PI at birth, while those with 2 mild CFTR variants (classes IV-VI) or with one severe and one mild variant are mostly pancreatic sufficient (PS) at birth. Symptoms of PI are not specific, including abdominal pain, chronic diarrhea, bloating, increased appetite contrasting with poor weight gain in children or weight loss in adolescents or adults. PI contributes to steatorrhea and negative energy balance, and thereby malnutrition, as well as to trace element and fat-soluble vitamin deficiency (A, D, E, K), and impaired bone health (14).

Pancreatic enzyme function can be assessed by a fat balance study with concomitant assessment of dietary fat intake and fat excretion in stools over 3 days, and determination of the coefficient of fat absorption. In infants <6 months of age, reference values are >85%, and above that age, reference values are >93% to 95%. This test is very cumbersome and time-consuming to perform in real-life conditions. Fecal pancreatic elastase-1 (FE1) is a simple and reliable marker of exocrine pancreatic function from two weeks of age onwards. FE1 concentration above 200 μg/g stool is normal, while FE1 concentrations below 100 and between 100 and 200 μg/g stool are respectively indicative of severe PI and inconclusive. FE1 concentration may be falsely low in case of diarrhea because of dilution. Some patients who are initially PS later become PI as CF disease causes progressive pancreatic damage. In PS patients, monitoring of pancreatic function by FE1 assessment is needed every year and in case of unexplained failure to thrive or weight loss (15).

Pancreatic enzyme replacement therapy (PERT) is essential to maintain adequate nutritional status in PI patients. PERT involves oral administration of pancreatic enzymes, especially protease and lipase, in order to have enzymes in the duodenal lumen for digestion of proteins and fat. Pancreatic enzymes are given orally, usually as enteric-coated porcine derived tablets or microspheres, thus preventing their inactivation by gastric acid. Of note, there is no PERT

derived from kosher or halal animals, and no approved PERT is vegan. The short-term effectiveness of PERT is well established in clinical practice. However, there is no evidence on the optimum time to start PERT, doses of enzymes needed for patients with different levels of severity of PI, and variations based on differences in meals and meal sizes (16,17). More data from interventional trials are needed. Consensus guidelines on nutrition care for infants, children, and adults with CF have been published jointly in 2016 by the European Society for Clinical Nutrition and Metabolism (ESPEN), the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), and the European Cystic Fibrosis Society (ECFS) (18). Table 1 shows the recommended doses for lipase intake by age of the patient, by body weight and by grams of fat ingested per day. The help of a dietitian is recommended to improve the management and nutritional care of a patient presenting with CF and PI (19). Fat soluble vitamin supplementation should be given to all PI patients in addition to PERT (15).

For patients of all ages, the main concern associated with PERT is poor growth and/or loss of weight, the most common reasons being low compliance to PERT and/or mishandling of PERT. Even if the evidence is weak, addition of acid suppression agents (H2 receptor antagonists and proton pump inhibitors (PPIs)) may improve effectiveness of PERT in patients with CF and persistent malabsorption despite adequate PERT dose (20). There is no evidence for the management of PERT during enteral tube feeding. The use of polymeric feeds necessitates PERT, as do semi-elemental feeds given to severely PI patients, with dosing and timing individually tailored. Most CF centers recommend giving half the required dose of PERT at the beginning of feeding and the second half at the end of feeding. Whatever the age, powder enzymes can also be used to digest enteral tube feeding, *e.g.* when administration of oral enzymes is not possible, or when jejunostomy feeds are required. Powder enzymes should be given as bolus doses through the feeding tube. When unprotected powder enzymes are used, addition of a PPI may help to prevent destruction of lipase by gastric acid. Excessive doses of PERT may result in constipation and abdominal pain. Alternatives to porcine-derived PERT are currently under evaluation. Liprotamase is a biotechnology-derived combination of crystalline lipase, crystalline protease, and amorphous amylase. The open-labeled phase III study suggested that the product was safe and associated with age-appropriate weight gain or maintenance in CF patients with PI. However, FDA declined to recommend lipromatase for PI in 2019 (15).

A syndrome named fibrosing colonopathy was described in the early 1990's. Some patients with CF presented with abdominal pain, constipation or occlusion, and often blood in the stools. Fibrosing colonopathy was characterized by extensive transmural fibrosis and impressive hypertrophy of the muscularis mucosae. Available evidence suggested the responsibility of very high doses of pancreatic supplements, sometimes over 50,000 units of lipase per kilogram body weight per day. Fibrosing colonopathy has disappeared shortly after implementation of the recommendation for an upper limit of 10,000 units of lipase/kg/day (14).

GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease (GERD) is more frequent in patients with CF than in the general population. The prevalence of GERD depends on the diagnosis method used. Using impedance and pH monitoring, GERD has been found in up to 67% of pediatric and 87% of adult patients with CF (21). Acidic GER is the most frequent but duodeno-gastroesophageal

reflux has been detected in around one third of adult patients with CF. Many risk factors for GERD in CF have been suggested: increased number of transient lower esophageal sphincter relaxations, increased gastroesophageal pressure gradient due to lower inspiratory intrathoracic pressure, delayed gastric emptying, high fat diet, chronic cough, chest physiotherapy, underlying lung disease, and treatment with beta-2 adrenergic agonists. Abnormalities of esophageal and gastric motility in patients with CF have been recently reviewed (22). Patients with CF and GERD have more infectious exacerbations and a lower pulmonary function. However, whether there is a causal relationship between presence and/or severity of GERD and decline in lung health is controversial. GERD is suspected to play a role in a higher risk for allograft rejection after lung transplantation. The use of a PPI is the usual first choice of treatment, but it is associated with an increased risk of small intestinal bacterial overgrowth as well as of respiratory and GI infections (14). Long-lasting GERD is a risk factor for Barrett's esophagus and esophageal cancer (see below) (23).

CONSTIPATION

Constipation is common in patients with CF. Constipation has been defined by the ESPGHAN Working Group on Cystic Fibrosis as (1) abdominal pain or distension or both or (2a) a decline in the frequency of bowel movements in the last few weeks to months or (2b) increased consistency of stools in the last few weeks or months or both, whereas (3) the symptoms are relieved by the use of laxatives (*e.g.* polyethylene glycol) (24). Adequate hydration and regular physical exercise are useful. Owing to the slow transit time and high stool viscosity in CF, fiber supplementation may worsen constipation in some patients and be responsible for bloating and flatulence. Enemas are rarely needed.

DISTAL INTESTINAL OBSTRUCTION SYNDROME

Distal small bowel obstruction syndrome (DIOS) caused by meconium-like stool plugs occurs at any age after the neonatal period, affecting up to 15-20% of patients with CF and about half of those with a history of MI (25). The incidence of DIOS is similar in children and adults. DIOS is characterized by the accumulation of viscid fecal and sticky mucoid intestinal content within the lumen of the terminal ileum and caecum, thus leading to incomplete or complete intestinal obstruction. Risk factors for DIOS are severe genotype (class I-III variants), PI, dehydration, poorly controlled fat malabsorption, history of MI and/or DIOS, CF-related diabetes, and organ transplantation (26). However, the pathophysiology of DIOS is still poorly understood (22).

The ESPGHAN Working Group on Cystic Fibrosis defined complete and incomplete DIOS as specific and distinctive from constipation. DIOS has an acute onset of symptoms as opposed to constipation. Complete DIOS is defined as a combination of (1) complete intestinal obstruction, with bilious vomiting and/or fluid levels in the small intestine on X-ray and (2) a fecal mass in ileo-caecum and (3) abdominal pain or distension or both. Incomplete or impending DIOS is defined as (1) a short history (days) of abdominal pain or distension or both and (2) a fecal mass in ileo-caecum, but without signs of complete obstruction (Figures 4 and 5) (24). Differential diagnoses include appendicitis, volvulus, intussusception, adhesions, and malignancy.

There is a lack of evidence for the prevention and treatment of DIOS in patients with CF (27,28), that are therefore largely empirical. Oral rehydration combined with stool softeners

containing polyethylene glycol (PEG) are usually effective in patients with incomplete DIOS. A ready-to-use iso-osmotic PEG solution is given at a dose of 20-40 mL/kg/h up to a maximum of 1 L/h over 8 hours. An alternative is the use of Gastrografin® either orally or *via* nasogastric tube if needed, at a dose of 50 mL in 200 mL of water/juice for children <6 years and 100 mL diluted in 400 mL for older patients on the first day, and half doses on following days if necessary (29).

In patients with complete DIOS, intestinal lavage with a balanced electrolyte iso-osmotic PEG solution as mentioned above is generally used as a first step, either orally or *via* nasogastric tube. In case of bilious vomiting, or when washout therapy has failed, hospitalization is needed and IV rehydration and nasogastric aspiration commenced. Gastrografin® can be used by enema (100 mL diluted four times with water) under the control of an experienced radiologist. Gastrografin® may cause considerable fluid shift from the circulation to the bowel and severe complications have been reported, including shock, intestinal perforation and enterocolitis.

Surgery should be considered only in extreme situations. Laparotomy with washout *via* enterostomy should be tried before considering resection of the ileo-caecum (29).

RECURRENT PANCREATITIS

Patients with CF may develop a single episode of acute pancreatitis or more frequently acute recurrent pancreatitis (ARP). In a large cohort of more than 1,000 patients with CF followed over a period of 30 years, the incidence of pancreatitis was 1.7% (30). ARP may occur in about 20% of patients with CF and PS and in less than 1% of those with CF and PI. There is a positive correlation between ARP, PS and mild CFTR variants (class IV-VI): the milder the variants the higher the risk for ARP (31). ARP may lead over time to chronic pancreatitis with calcifications(Figure 6), progressive destruction of the exocrine pancreas and secondarily PI (13). Clinical presentation and treatment of acute pancreatitis in patients with CF are not different from those in the general population (32,33), and the use of a low-fat diet in the context of CF-associated pancreatitis is not advisable. Observational studies indicate that unaffected relatives of CF patients frequently present with chronic pancreatitis or ARP. These patients are two to three times more likely to be heterozygous for CF mutations than the general population. The diagnosis work-up of a patient with chronic pancreatitis suspected to be of genetic origin should comprise not only testing for cationic trypsinogen (PRSS1), serine protease inhibitor Kazal 1 (SPINK1) and chymotrypsinogen C (CTRC) but also for CFTR (32).

CANCER

Because of increased life expectancy, most patients with CF are now expected to live to or beyond their fifties, when cancer is more frequent. In addition, epidemiologic studies have shown that CF is associated with a higher risk for GI malignancy as compared with the general population. Colorectal cancer (CRC) is the most common GI cancer and represents the most significant risk with up to 50% of patients with CF older than 40 years diagnosed with adenomatous polyps and up to 25% with advanced adenomas (34). The risk is higher in male patients, those with PI, a history of DIOS or CF-related diabetes, and severe CF variants as p.Phe508del homozygosity.

Several factors are likely to play a deleterious role. Impairment in the CFTR protein causes mucosal obstruction and inflammation. Chronic GI inflammation, as demonstrated in patients with CF by video-capsule endoscopy abnormalities of the small bowel and increase of the fecal

calprotectin concentrations, may cause direct damage to epithelial cells and bacterial dysbiosis, thus promoting oncogenesis. At the molecular level, absence of CFTR function causes upregulation of oncogenic genes. CFTR-knockout mice have an increased incidence of CRC compared with wild-type mice, and dysregulation of genes associated with immune responses and intestinal stem cells regulation. Repeated exposure to radiation (*i.e* X-rays and CT scans) may also play a deleterious role (35).

A systematic review and meta-analysis of the risk of GI cancer in patients with CF showed that the overall risk of GI cancer was eight times higher than in the general population (35). The risk for the following site-specific cancers was also significantly increased in patients with CF compared with the general population: multiplied by 10 for CRC, 18 for small bowel cancer, 6 for pancreatic cancer, and 17 for biliary tract cancer. The risk for GI cancer among transplanted patients with CF was five times higher than in those who did not receive a transplant. With the aim to decrease this excess risk of CRC in patients with CF, the CF Foundation asked a task force to develop colonoscopy-based screening recommendations (36). For non-transplanted patients, colonoscopy should start at age 40 years, with 5-year re-screening and 3-year surveillance intervals in patients who have adenomas (unless shorter interval is indicated by individual findings). Transplanted patients should start CRC screening within 2 years of the transplantation because of the additional risk for CRC associated with immunosuppression. Because of the likelihood of retained feces in patients with CF, intensive bowel preparation is recommended prior to colonoscopy in order to allow for optimal examination.

Guidelines for screening hepato-pancreato-biliary cancers have been proposed (37). Suggested timing for the initiation of screening in patients with CF is 40 years and within 2 years after transplantation in transplanted patients. Several screening methods have been listed as measurement of CA-19-9, abdominal ultrasound, magnetic resonance cholangiopancreatography or endoscopic ultrasonography. The proposed screening interval is every 2-3 years in non-transplanted patients and every 1-2 years in transplanted patients. Although the relative risk of these cancers is elevated in patients with CF compared with the general population, the absolute risk remains low and screening is not yet recommended in the CF population (37).

A recent case-control study showed that patients with CF had a three-fold increased risk for Barrett's esophagus or related neoplasia. Mean age at diagnosis was 36 years, much younger than the age at which Barrett's esophagus is generally diagnosed in the general population. Upper GI endoscopy should be considered in patients with CF presenting with long-standing GERD, and could accompany age-appropriate screening colonoscopy (23).

MISCELLANEOUS

Clostridium difficile infection

Carriage of *Clostridium difficile* (*C. difficile*) and presence of *C. difficile* toxin in stool ranging from 20 up to 50% has been reported in patients with CF, to be compared with around 2-3% in the healthy adult population. However, symptomatic *C. difficile* infection is rare, possibly due to the inactivation of CFTR-related intestinal Cl-secretion. Hospitalizations, use of PPIs and cumulative exposure to IV antibiotics are risk factors for *C. difficile* infection. Screening for *C. difficile* in the absence of symptoms is not common practice and the need for eradication of *C. difficile* is not yet demonstrated (14).

Intussusception

Intussusception may occur in patients with CF and PI (Figure 7). The lead point of the intussusception is usually an intraluminal muco-fecal mass located in the ileocolonic region. Ultrasound examination has an excellent sensitivity and specificity. Surgery is only indicated when hydrostatic reduction is unsuccessful (14).

Acute appendicitis

The incidence of acute appendicitis is considered to be lower in patients with CF, and symptoms may be attenuated because of long-term exposure to antibiotics (38). Therefore, diagnosis may be delayed or confused with DIOS, and complications more common, as appendiceal perforation, appendiceal abscess (Figure 8), and peritonitis.

Small intestinal bacterial overgrowth

Small intestinal bacterial overgrowth (SIBO) is often suspected in patients with CF. Risk factors include: 1) thickened GI mucus that retains bacteria on the intestinal surface; 2) dysmotility with delayed gastric emptying and abnormalities of the small bowel transit (39,40); 3) recurrent antibiotic treatments for pulmonary exacerbations; 4) intestinal inflammation; 5) previous intestinal surgery (8). Symptoms associated with SIBO are numerous and non-specific, as abdominal pain, diarrhea, bloating, flatulence, excessive bowel gas, and intestinal malabsorption despite adequate PERT. Hydrogen and/or methane breath test after ingestion of lactulose or glucose is difficult to interpret. Empiric treatment is often initiated with laxatives (PEG) and/or oral antibiotics active on anaerobic and gram-negative bacteria as metronidazole, rifaximin or amoxicillin/clavulanate (8,41). There is no evidence on the duration and need for cyclical administration of oral antibiotics. The efficacy of prebiotics, probiotics or symbiotics remains to be demonstrated.

Appendiceal mucocele

Appendiceal mucocele is suspected in case of recurrent abdominal pain with a concomitant mass in the lower inferior quadrant of the abdomen. Ultrasonography will confirm the diagnosis. Appendectomy with resection of the appendix edges and resection of the cecal tip will prevent from recurrence. Appendiceal mucocele can be diagnosed fortuitously on ultrasound of the abdomen. In the absence of symptoms, there is no need for systematic surgery (14).

Rectal prolapse

Rectal prolapse was frequently observed in CF patients several decades ago and could be the revealing symptom of the disease. Nowadays, rectal prolapse is quite unusual in patients with CF, most probably because of earlier diagnosis through NBS and better management of PI. Rectal prolapse may still be observed in a few PI patients with severe malnutrition and/or poor compliance to PERT (14).

Lactose intolerance

CF does not seem to be associated with a higher risk for lactose intolerance (7). The interpretation of a lactose breath hydrogen test may be difficult in patients with CF since baseline breath hydrogen may be elevated, and small intestinal bacterial overgrowth may give a false-positive result (14).

Inflammatory bowel disease

A prospective survey of about 11,000 US patients with CF published in the mid-1990's concluded that the prevalence of inflammatory bowel disease (IBD) and Crohn's disease was respectively 7- and 17-fold higher in patients with CF than in the general population (42). However, confirmation from larger epidemiological studies is still awaited. The presence of non-specific digestive symptoms (diarrhea, abdominal pain) and failure to thrive in young patients with CF, as well as intestinal inflammation often seen in CF, may have contributed to an overdiagnosis of IBD.

Celiac disease

A recent systematic review and meta-analysis concluded that the prevalence of celiac disease in patients with CF seemed to be more than twice as high compared to the general population (43). However, there is no consensus as to whether patients with CF should be screened for celiac disease. Celiac disease should be assessed in patients with CF who have persistent GI symptoms despite adequate care and PERT. Caution is needed in the interpretation of elevated anti transglutaminase-IgA as CF is associated with a high prevalence of autoantibodies, possibly related to chronic inflammation. A diagnosis of celiac disease suggested by a positive serological screen needs intestinal biopsy to be performed.

Peptic ulcer disease

Gastric hypersecretion and decreased bicarbonate production due to PI could increase the risk for peptic ulcer disease in patients with CF (14). However, confirmation from epidemiologic studies is still pending.

TRANSITION

In health care, the term 'transition' is used to describe the process of transferring from child to adult health care services. Because this period of transition during late adolescence or early adulthood coincides with physical and psychosocial changes, compliance to therapy may be compromised with risk of both impaired lung health and nutritional status (1). Key features for a safe transition include an early preparation, planning and self-management skills, a coordinated approach and a detailed communication between patients, families, pediatric and adult teams. The adult multidisciplinary CF team should comprise a gastroenterologist with expertise in the care of patients with CF (1).

CFTR MODULATORS

The 2020's represents a new era for patients with CF and health care providers, with the increasing availability of molecules aimed at correcting the defective CFTR protein and referred to as CFTR modulators. This therapeutic approach addresses the actual defect in chloride transport and is "personalized" since the molecules given to patients depend on the type of CFTR variants they carry. According to the CF Foundation, "this medicine represents the single greatest therapeutic advancement in the history of CF, offering a treatment for the underlying cause of the disease that could eventually bring modulator therapy to 90 percent of people with CF." Three main groups of molecules have been developed: 1) potentiators that improve the function of CFTR protein at the cell surface; 2) correctors that help trafficking

of CFTR to the cell surface and; 3) amplifiers that increase the amount of CFTR mRNA (and therefore protein) within the cell (44).

The first CFTR modulator, the potentiator ivacaftor (IVA - Kalydeco®) was approved in 2012 for patients with at least one variant G551D or other class III variants, and it is now used for more than 90 CFTR variants (45). The impact on pulmonary exacerbations, respiratory function, body weight, and pancreatic exocrine function is significant. The combination of ivacaftor with a corrector (lumacaftor LUM/IVA - Orkambi®) was approved in 2015 for patients aged ≥12 years homozygous for p.Phe508del, *i.e.* around 50% of patients with CF. Orkambi® is now available for use down to 2 years in the US and 6 years in Europe. Another second combination with a corrector (tezacaftor/IVA - Symdeko® in the US/Symkevi® in Europe) was approved thereafter for the same type of patients. The combination of ivacaftor with two correctors (elexacaftor/tezacaftor)/IVA) was last approved for the treatment of patients aged ≥6 years in the US and ≥12 years in Europe carrying at least one variant p.Phe508del, *i.e.* 80-90% of patients with CF. This combination (Trikafta® in the US/Kaftrio® in Europe) also results in significant improvements in lung function, pulmonary exacerbations and quality of life (46).

CFTR modulators also have extrapulmonary effects although the evidence is still weak, owing to small sample sizes, low number and short duration of available studies (47). If ductal blockages can be relieved before the destruction of distal pancreatic tissue, digestive enzymatic secretion may potentially be recovered. The improvement in FE-1 concentration observed in infants aged 4 to 12 months and in children aged 1-5 years after IVA or LUM-IVA treatment, as well as several case reports describing the reversal of documented PI, including in older children taking IVA, suggest that pancreatic damage can be reversible (6,48). A reduction in the rate of hospitalizations related to pancreatitis episodes and decreased opioid use was also observed, possibly related to a reduction of pancreatic ductal mucoid obstruction (49). Small observational studies suggested a reduction of patient-reported GERD symptoms over 1 year of IVA; an alkalinization of intestinal pH that may enhance pancreatic enzyme function; and lower fecal calprotectin concentrations reflective of reduced intestinal inflammation in association with increased abundance of *Akkermansia*, a bacteria associated with reduced intestinal inflammation. Further studies are needed to confirm whether CFTR modulators have a positive impact on exocrine pancreatic function, intestinal pH and inflammation.

CONCLUSION

CF has become a chronic disease of adulthood with many digestive outcomes, and expertise from gastroenterologists in CF care is needed. The treatment of CF has moved from a therapy treating symptoms to a personalized and targeted therapy that also restores the function of the CFTR protein. The increasing use of CFTR modulators is expected to further improve patient survival in the coming years.

PRACTICE POINTS

- CF is no longer an exclusive pediatric disease but a disease predominant in adults.
- Following the lung, the pancreas is most frequently impacted organ in CF.
- Increased life expectancy leads to a higher risk for GI malignancy, especially CRC.

- CFTR modulators have transformed the prognosis of CF.
- Every CF Center should comprise a gastroenterologist with expertise in the care of patients with CF.

RESEARCH AGENDA

- More data are needed on the prevalence of GI manifestations, with a focus on adult patients.
- A better knowledge on pathophysiology of GI manifestations, especially in relation to dysmotility, dysbiosis and inflammation, would help prevention and treatment.
- The impact of CFTR modulators on the prevention and treatment of GI manifestations needs to be clarified.

CONFLICT OF INTEREST

None.

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Figure 1. Functional classification of CFTR variants.

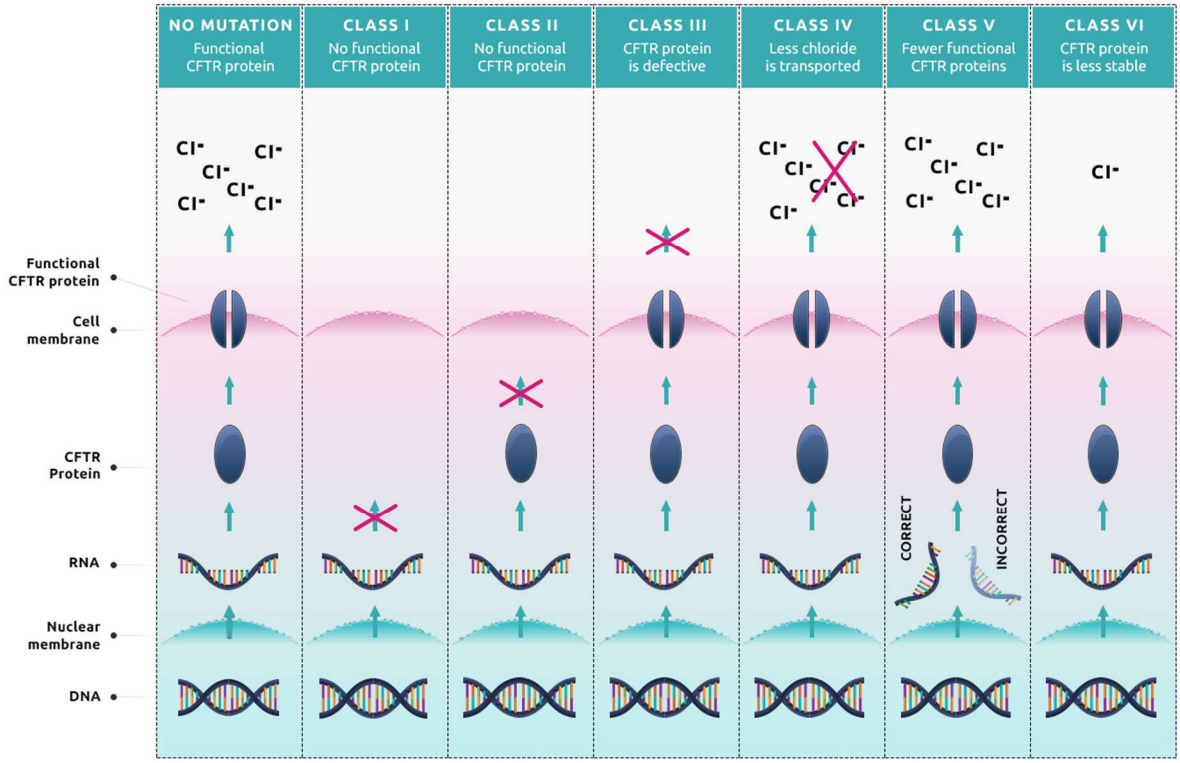

Figure 2. Fatty infiltration of the pancreas. Ultrasound in a 34-year-old woman with CF shows a hyperechoic pancreas.

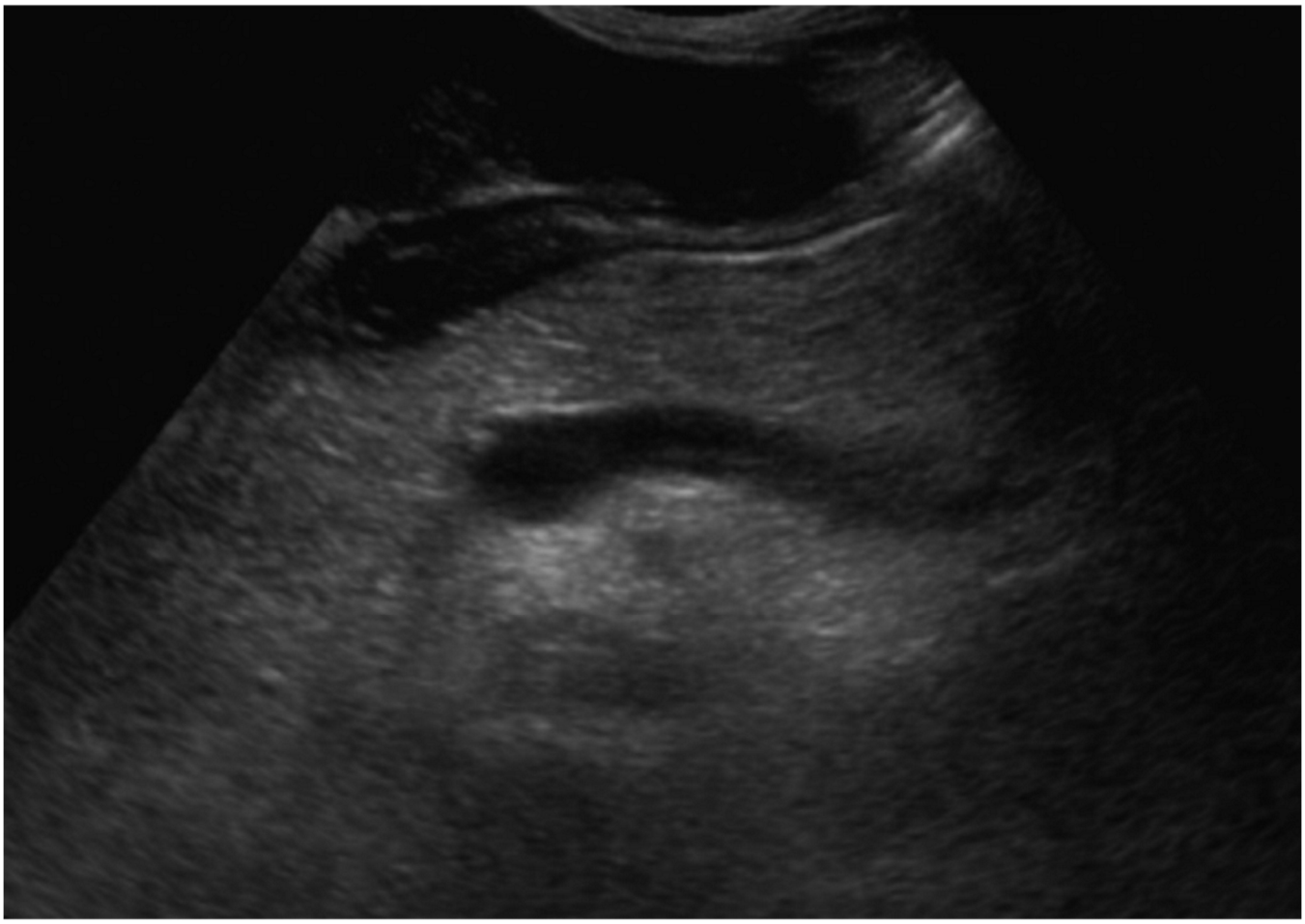

Figure 3. Fatty infiltration of the pancreas. Computerized Tomography (CT) scan in a 34-year-old woman with CF shows complete fatty replacement of the pancreas.

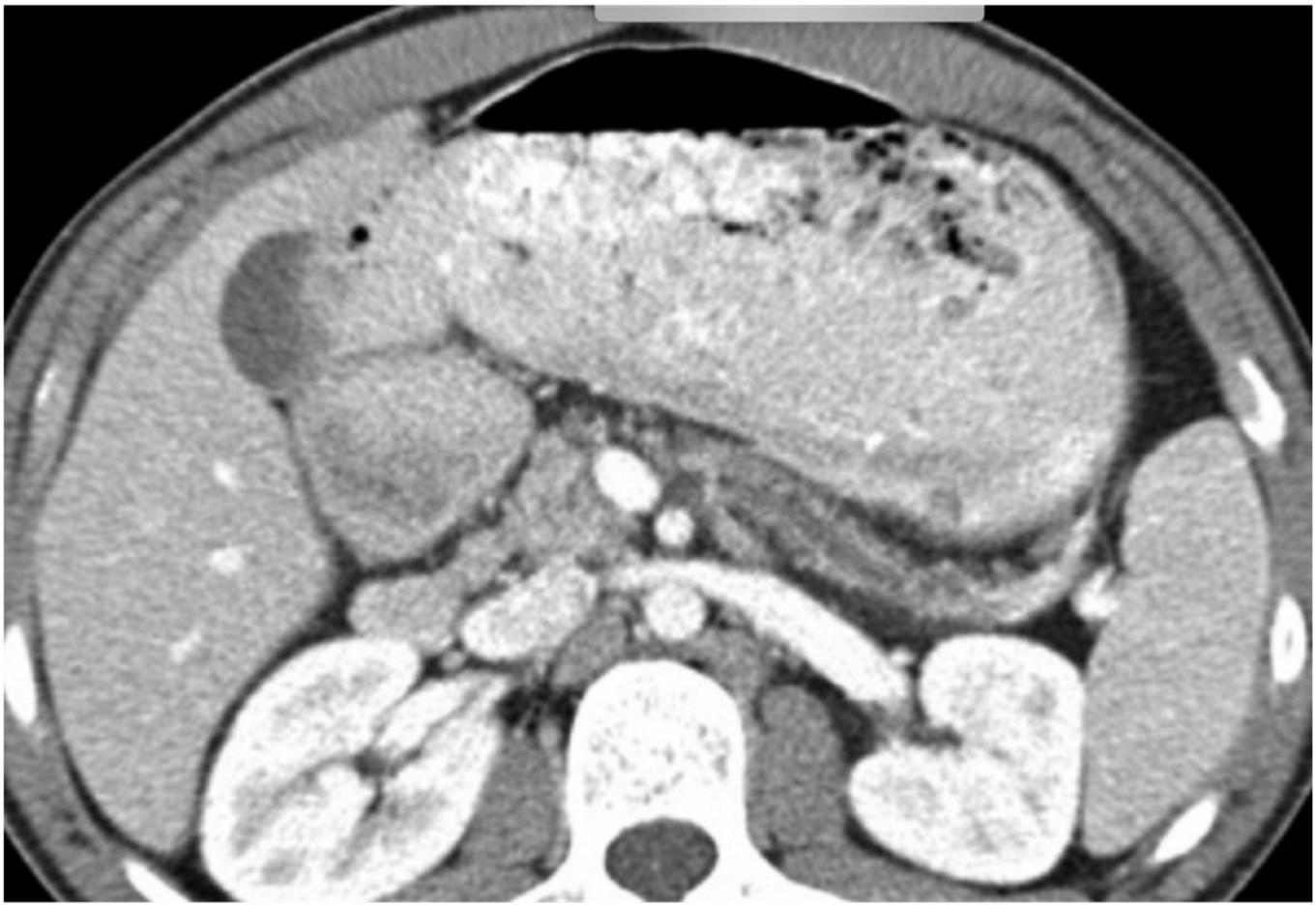

Figure 4. Distal intestinal obstruction syndrome (DIOS). CT scan in a 26-year-old woman with CF shows small bowel obstruction secondary to impacted fecal material (arrow) in the right lower quadrant.

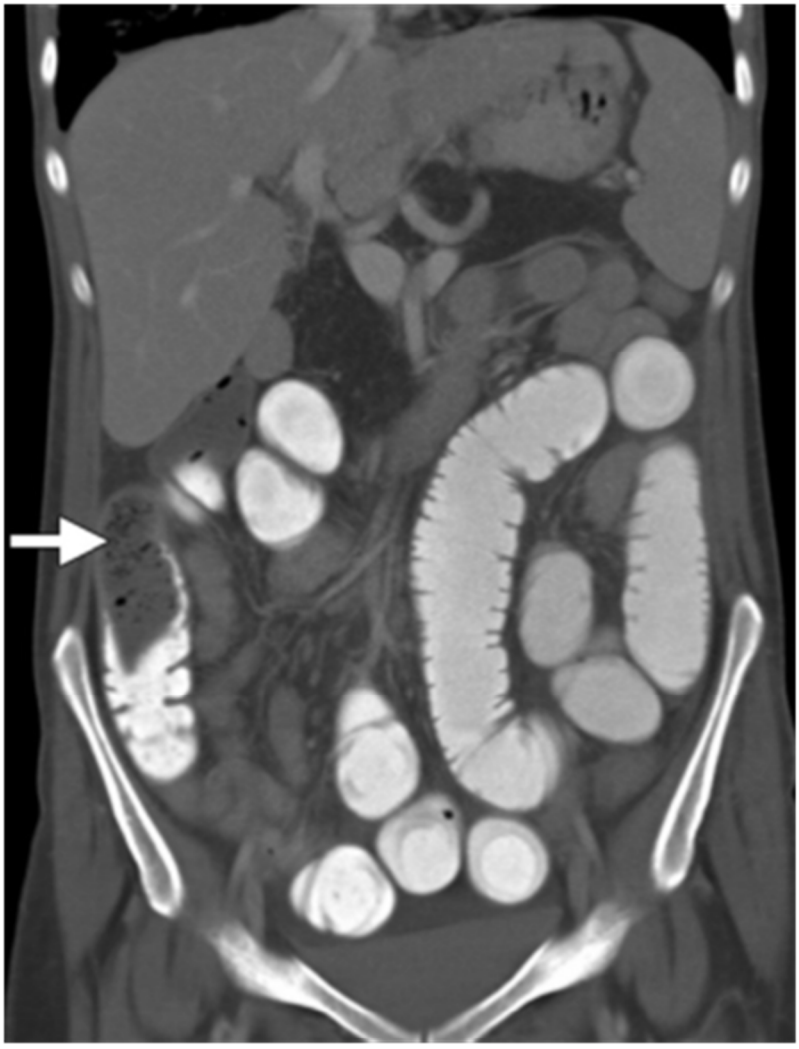

Figure 5. Distal intestinal obstruction syndrome (DIOS). CT scan in an adult patient with CF shows mucoid material (arrow) adherent to the small-bowel wall.

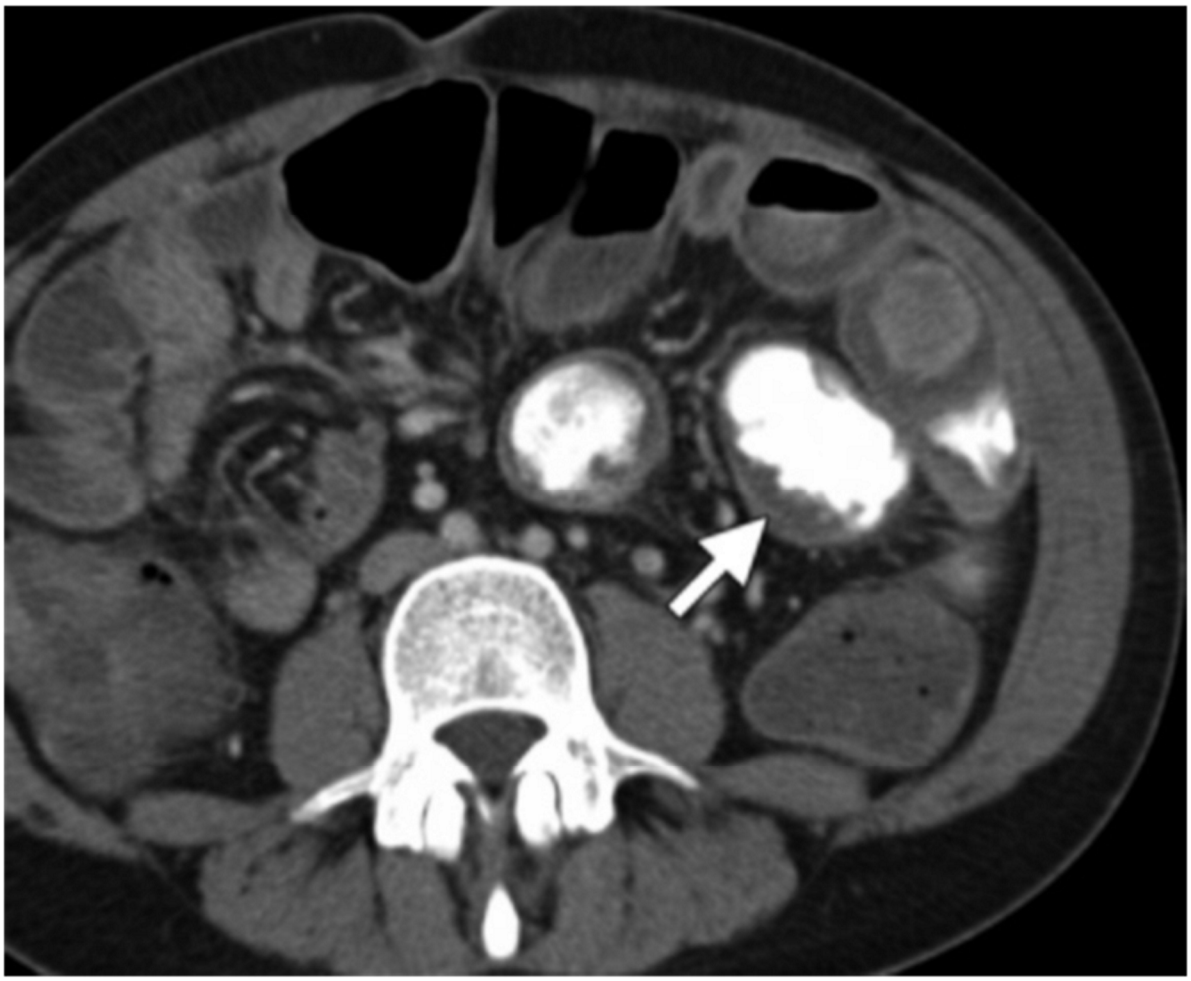

Figure 6. Pancreatic calcifications. CT scan in a 28-year-old man with CF and acute recurrent pancreatitis shows extensive pancreatic calcifications. Severe pancreatic atrophy is also present.

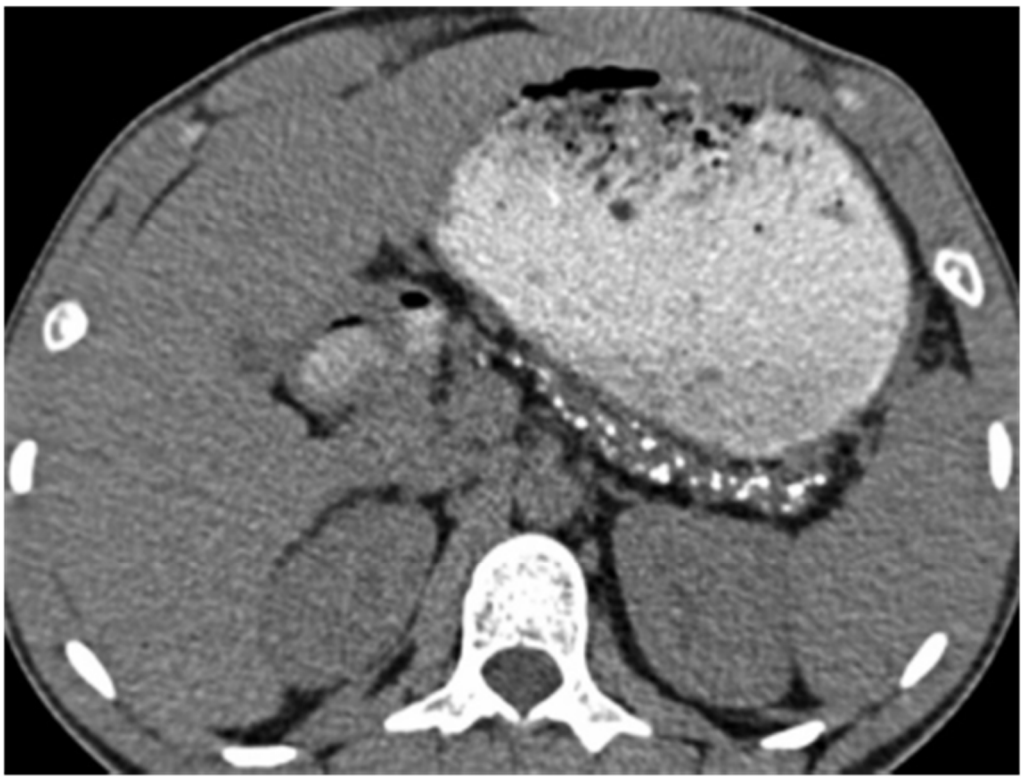

Figure 7. Intussusception. CT scan in a 27-year-old man shows intussusception (arrow) in a jejunal loop in the left upper quadrant, with the classic “target” sign or “donut” sign.

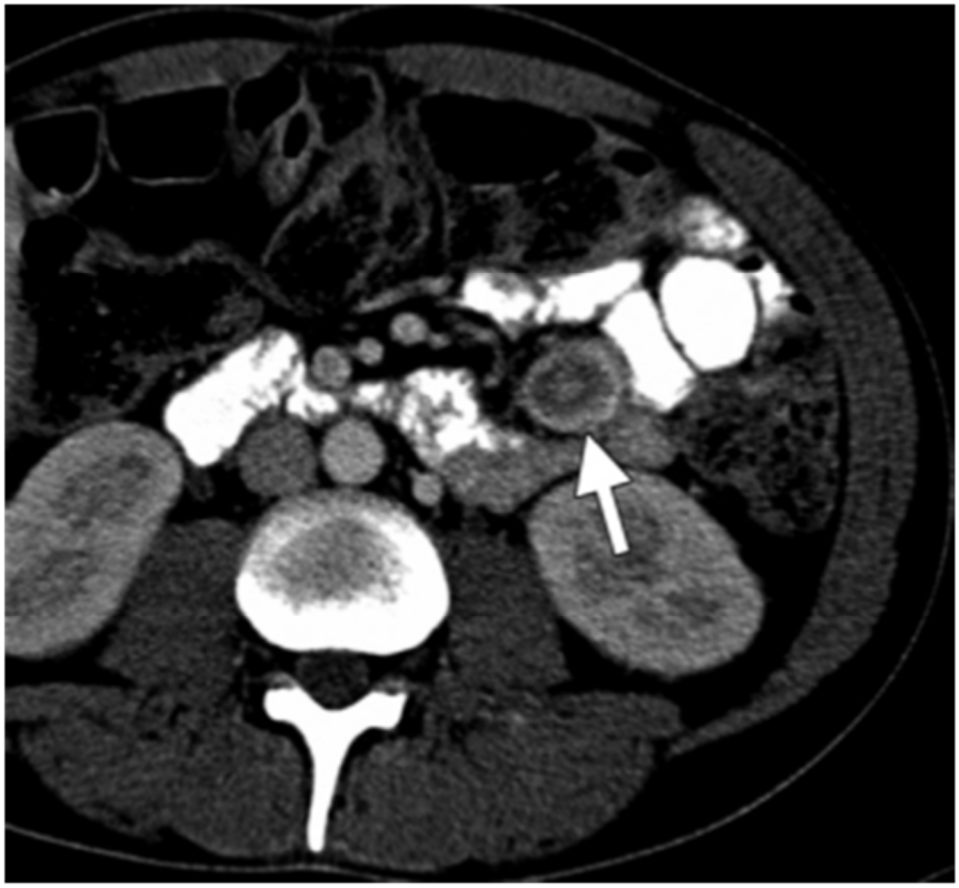

Figure 8. Appendiceal abscess. CT scan in a 25-year-old man with CF shows an appendiceal abscess (arrow) and adjacent fat stranding in the right iliac fossa.

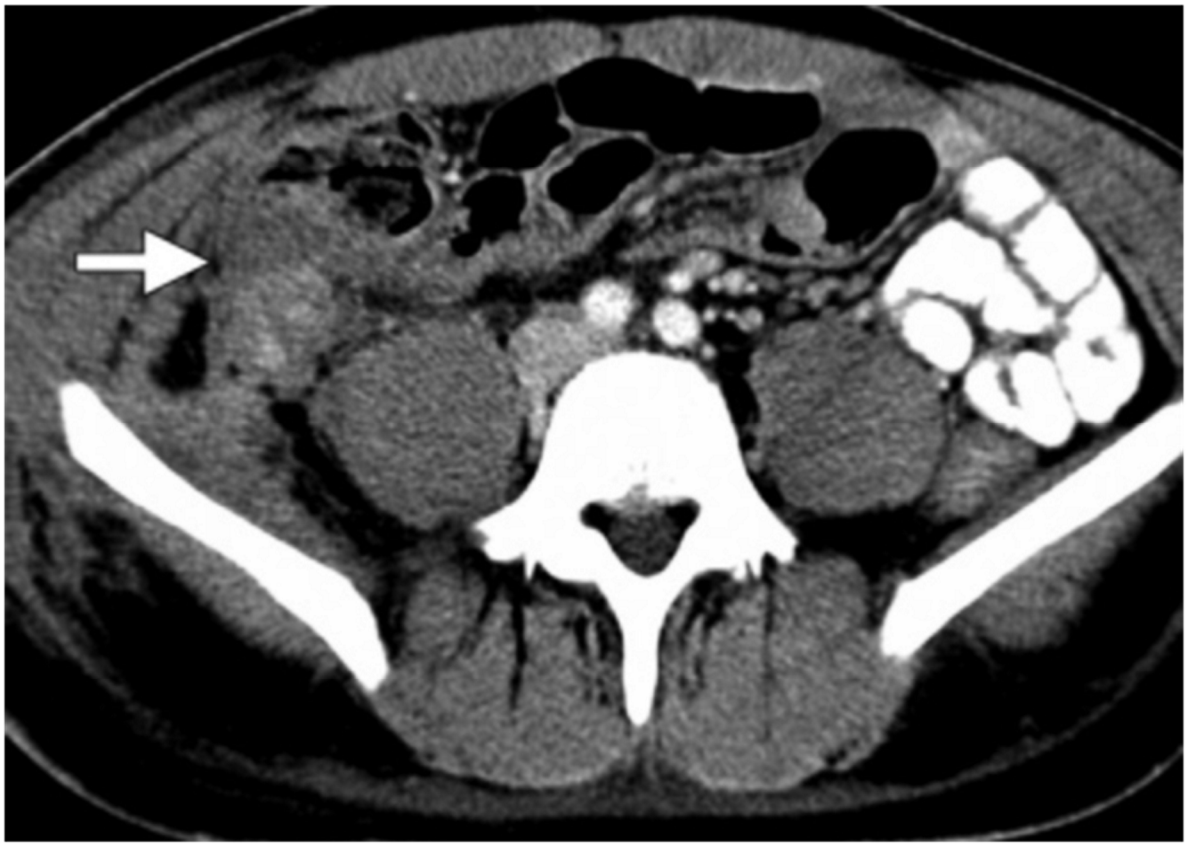

Table 1. ESPEN-ESPGHAN-ECFS recommended guidelines for pancreatic enzyme lipase replacement therapy (PERT) (*in* 18)

Age	Supplementation
Infants (up to 12 months)	2000-4000 U lipase /120 mL formula or estimated breast milk intake and approximately 2000 U lipase/gram dietary fat in food
Children 1-4 years	2000-4000 U lipase/gram dietary fat, increasing dose upward as needed (maximum dose 10,000 U lipase/kg/day)
Children >4 years and adults	Consider starting at 500 U lipase/kg/meal, increasing dose upward as needed to a maximal dose of: - 1000-2500 U lipase/kg per meal, or - 10,000 U lipase/kg/day, or - 2000-4000 U lipase/gram dietary fat taken with all fat-containing meal, snacks and drinks

Abbreviations:

- U: units
- ESPEN: European Society for Clinical Nutrition and Metabolism
- ESPGHAN: European Society for Paediatric Gastroenterology, Hepatology and Nutrition
- ECFS: European Cystic Fibrosis Society