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# Pancreatitis and pancreatic cystosis in Cystic Fibrosis

A. Jay Freeman [a,*], Chee Y. Ooi [b]

[a] Emory University School of Medicine/Children's Healthcare of Atlanta, 2015 Uppergate Dr. NE, Atlanta, GA 30322, United States
[b] School of Women's and Children's Health, Medicine, University of New South Wales and Sydney Children's Hospital Randwick, Sydney, Australia

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**Abstract**

The pathologic effects of an altered cystic fibrosis transmembrane receptor (CFTR) protein on the exocrine pancreas is ubiquitous and of varying severity. In this section, pancreatitis and pancreatic cystosis are covered.


*Keywords:* Pancreatitis; Pancreatic cystosis, cystic fibrosis; CFTR

## 1. Background

The pathologic effects of an altered cystic fibrosis transmembrane receptor (CFTR) protein on the exocrine pancreas is ubiquitous and of varying severity. In this section, pancreatitis and pancreatic cystosis are covered.

### *1.1. Pathophysiology*

#### *1.1.1. Pancreatitis in CF*

The development of symptomatic pancreatitis in patients with CF is uncommon. Although cases of pancreatitis in pancreatic insufficient (PI) patients exist [1–3], pancreatitis in CF is generally believed to occur exclusively within pancreatic sufficient (PS) patients, with ~20% of PS patients developing pancreatitis [4,5]. In the majority, damage to the pancreas begins in utero and often continues into infancy and early childhood, eventually resulting in PI from loss of acinar tissue (see Fig. 1) [6,7]. Only 1–2% of residual pancreatic reserve is required to maintain PS [8]. This process of pancreatic damage is detectable by the release of pancreatic protein trypsinogen into the blood stream, which forms the basis of newborn screening for CF. Symptomatic pancreatitis results from an intricate balance between the degree of pancreatic acinar reserve and severity of ductal obstruction, both of which are related to the severity of CFTR dysfunction but in opposing directions (Fig. 2). A "critical mass" of acinar tissue in the presence of ductal obstruction is required to elicit an episode of symptomatic pancreatitis, explaining why only a small proportion of CF patients develop clinical pancreatitis [9,10].

Impaired $HCO_3^-$ secretion also appears important in the development of pancreatitis. In non-CF mouse models, acinar exocytosis of zymogens is associated with acidification of the lumen secondary to impaired neutralization resulting from $HCO_3^-$ deficiency. Impaired control of luminal pH is believed to contribute to tissue damage and pancreatitis [11]. Furthermore, separate animal and human models have shown that CFTR $Cl^-$ channel and anion exchangers are inhibited by trypsin resulting in decreased luminal pH that could promote premature zymogen activation resulting in acute and/or chronic pancreatitis [12].

#### *1.1.2. CFTR impact on disease severity*

Mouse models utilizing both CFTR knockout ($CFTR^{-/-}$) and p.F508del mice have shown overexpression of pro-inflammatory cytokines genes within the pancreas resulting in a more severe acute pancreatitis after cerulean hyper-stimulation as compared to

* Corresponding author.
*E-mail address:* afreem6@emory.edu (A.J. Freeman).

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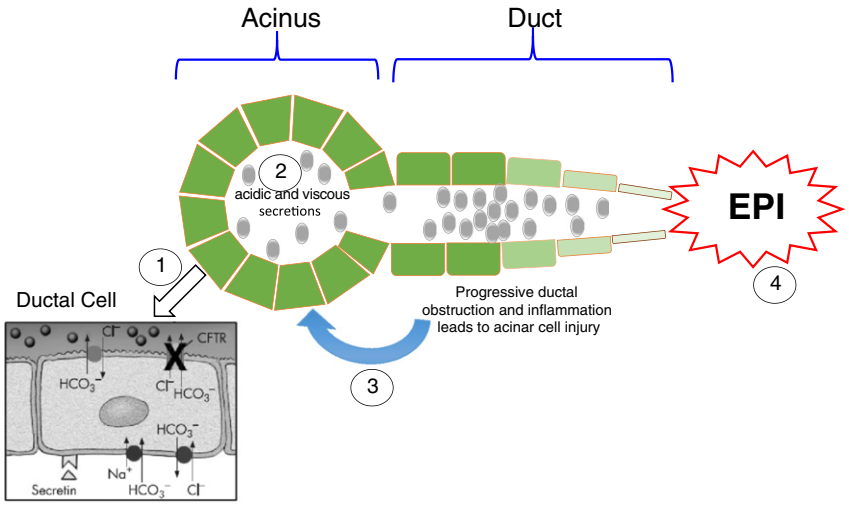


Fig. 1. Theorized mechanism for the progression of pancreatic damage resulting in pancreatic insufficiency in utero. Mutation in CFTR (1) impairs $HCO_3^-$ secretion which leads to acidic and viscous pancreatic secretions (2). This results in progressive ductal obstruction and inflammation (3) that causes acinar cell injury and ultimately, exocrine pancreatic insufficiency (4) (adapted from Wilschanski and Durie [10]).

wild type (WT) littermates [13,14]. Subsequent mouse models examining the role of Na+/H+ exchange regulatory factor-1 (NHERF-1) in acute pancreatitis showed that NHERF-1$^{-/-}$ mice expressed decreased levels of CFTR at the apical membrane of the pancreatic duct resulting in reduced fluid and $HCO_3^-$ secretion and a more severe acute pancreatitis. In total, these models suggest that CFTR is associated with the development of pancreatitis and influences severity through altered secretion of pancreatic fluid and $HCO_3^-$, rather than direct acinar cell or ductal injury.

### 1.1.3. Modifiers of CFTR

Interactions between CFTR and modifying intrinsic (e.g. genetics, bile) and extrinsic (e.g. smoking, alcohol) factors may influence the development of pancreatitis. A summary of these pancreatitis-influencing factors on CFTR is shown in Table 1.

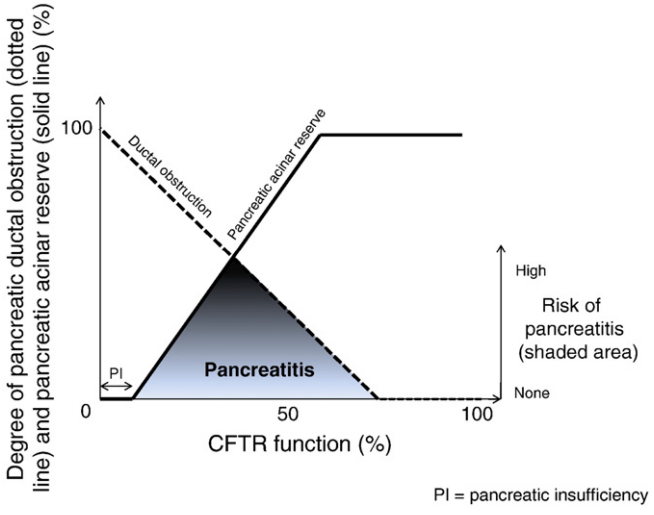


Fig. 2. Conceptual model demonstrating CFTR-related factors that contribute to pancreatitis. Development of pancreatitis is associated with the opposing factors of severity of ductal obstruction and degree of pancreatic acinar reserve. Adapted from Ooi et al. [5].

### 1.1.4. Genetics

Several reports have shown an increase incidence of CFTR mutations among patients with chronic pancreatitis (CP) and acute recurrent pancreatitis (ARP). In a study of 42 adolescents and adults with idiopathic ARP and CP, extensive CFTR genotyping identified 50% of patients with either 1 or 2 variants [15]. Among adult patients with CP or ARP, between 16 and 39% of patients have at least one CFTR mutation for an odds ration of ~3.0 compared to controls [16–18]. When those patients diagnosed with alcohol-induced pancreatitis were eliminated, the frequency has been reported as high as 60% [19]. Although genetic causes of pancreatitis are more common among children, the frequency of CFTR mutations is similar ranging from 19% to 48% among the relatively larger pediatric studies including the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) consortium database [20–22]. However, in only three of these studies were full CFTR sequencing performed for all patients [15,16,21]. This represents a major limitation as the highest risk mutations are associated with more mild CF disease that are often not picked up through standard screening panels and likely underrepresents the true incidence of CFTR mutations in these cohorts. This has resulted in the reporting of a relatively small number of CFTR mutations being reported; with non-CF causing mutations or mutations whose association to disease severity is unknown, likely being under recognized. The predominantly reported mutations include heterozygotes known to be associated with CF (e.g. p.F508del) or compound heterozygozity with a non-CFTR mutation associated with pancreatitis such as cationic trypsinogen (PRSS1), serine protease inhibitor Kazal 1 (SPINK1) and/or chymotrypsinogen C (CTRC) [16,17,19–21].

The risk of developing pancreatitis can be predicted using the pancreatic insufficiency prevalence (PIP) score [5,23]. The PIP score was developed and validated to categorize CFTR mutations according to predicted severity of mild vs.

Table 1
Modifying factors of CFTR-associated pancreatitis.

| Factor | Influence on CFTR |
|---|---|
| Ethanol | • Decreased CFTR expression and function<br>• Increased protein turnover<br>• Aberrant protein folding |
| Fatty acids | • Decreased CFTR expression and function<br>• Increased protein turnover<br>• Aberrant protein folding<br>• Decreased secretin-stimulated pancreatic fluid secretion |
| Bile acids | • Decreased CFTR function<br>• Theorized Decreased CFTR dependent $HCO_3^-$ secretion |
| Smoking | • Impaired secretin-stimulated pancreatic fluid secretion<br>• Inhibited CFTR function<br>• CFTR internalization and insolubility |

Summarized from the following sources [13–20].

moderate-severe mutations [5]. This study observed that the severity of CFTR genotype was strongly associated with the risk of pancreatitis, with 70% of PS CF patients who had a mild genotype developing pancreatitis compared to 30% with moderate-severe genotypes. The authors further found the risk of developing pancreatitis among those patients with a mild genotype was 71% greater than those in the moderate-severe group [5]. A comprehensive list of PIP scores is available [9].

Despite the very high risk of developing pancreatitis associated with milder CFTR genotypes, the fact that not all of these patients develop pancreatitis, and the variable phenotypic expression even among patients with the same mutation(s), lends more evidence that mutations in CFTR alone is not sufficient and requires additional "hits" or modifiers for the development of pancreatitis [4,24]. Pancreatitis modifiers would be expected to be the same as seen in non CF-associated pancreatitis and differ between adults and children as shown in Fig. 3. Infection-related [25] and drug-induced [26,27] pancreatitis episodes have also been reported in patients with CF.

## 2. Clinical presentation and differential diagnosis

The presentation of pancreatitis in patients with CF is no different than that in the general population. Acute pancreatitis (AP) is defined by at least two of the following three criteria being met: (1) upper abdominal pain with/without emesis; (2) amylase and/or lipase $\geq 3\times$ the upper level of normal; and/or (3) abdominal imaging consistent with pancreatitis [28,29]. ARP is defined as $\geq 2$ episodes of AP with a return to baseline between events. The diagnostic criteria for CP is evolving but currently accepted definition requires either: (1) chronic abdominal pain plus characteristic imaging findings of CP; (2) exocrine insufficiency plus imaging findings; or (3) endocrine insufficiency plus imaging findings [30,31]. Pancreatitis may also be the initial or sole manifestation of CF prior to its diagnosis [5,15,32]. Furthermore, patients with CF who present with pancreatitis may have a single-organ phenotype only [22] and lower sweat chloride values than those without pancreatitis [5].

The diagnosis of pancreatitis may be missed due to its relatively low frequency combined with a broad differential of more common causes of abdominal pain in CF (e.g. constipation, distal intestinal obstruction syndrome, intussusception, small bowel bacterial overgrowth). Approximately 20% of PS CF patients will develop pancreatitis during their lifetime, typically developing in their teens or adulthood [5,33]. Of these patients, only 18% will experience a single episode of AP while 60% will develop ARP with the remaining 22% advancing to CP [5].

## 3. Management and complications of disease

Specific guidelines for the management for pancreatitis in patients with CF do not yet exist; therefore, age-appropriate general pancreatitis management guidelines should be used as a general reference. It is suggested that an age-appropriate gastrointestinal (GI) expert is consulted for any episodes of pancreatitis.

### 3.1. Acute pancreatitis

Well-established guidelines exist for the management of acute pancreatitis (AP) in adults but are lacking in children. Initial management focuses on supportive care with vigorous fluid resuscitation, correction of electrolyte and metabolic imbalances, oxygen as required and of critical importance, adequate pain control [34,35]. Although various predictors of severity have been developed in adult [36] and pediatric [37–39] patients with acute pancreatitis, there has been none developed specifically for the CF population. Patients are generally "gut-rested" but reintroduction of enteral nutrition within 24–72 h should be strongly considered [40,41]. For patients experiencing their first episode of AP, imaging with an abdominal ultrasound is often indicated to rule-out gallstones or fluid collections [34,35]. Smoking and alcohol cessation should be advised where appropriate in order to help prevent reoccurrences [42]. The assessment of disease severity as well as consideration of pancreatitis-associated complications such as necrosis, pseudocyst management, and surgical or ERCP indications should be role of the consulting gastroenterologist.

### 3.2. Acute recurrent and chronic pancreatitis

Episodes of AP are treated as discussed above. For any patient experiencing two or more episodes of "idiopathic" AP or CP, a causal evaluation should be performed [34,43]. Sweat testing is recommended as first-line for evaluation of CF but nasal potential difference testing and CFTR gene sequencing should also be considered [30,35,44,45]. Genetic testing for PRSS1, SPINK1 and CTRC and assessment of anatomy with advanced imaging (e.g. CT, MRI, ERCP, EUS) should be strongly considered [43,46]. Recent recommendations from the INSPPIRE consortium support MRI/MRCP for all children undergoing a workup for ARP, acute increase in direct bilirubin and/or GGT $>2\times$ ULN. ERCP, and EUS may be reasonable alternatives depending on the clinical situation [40]. Although

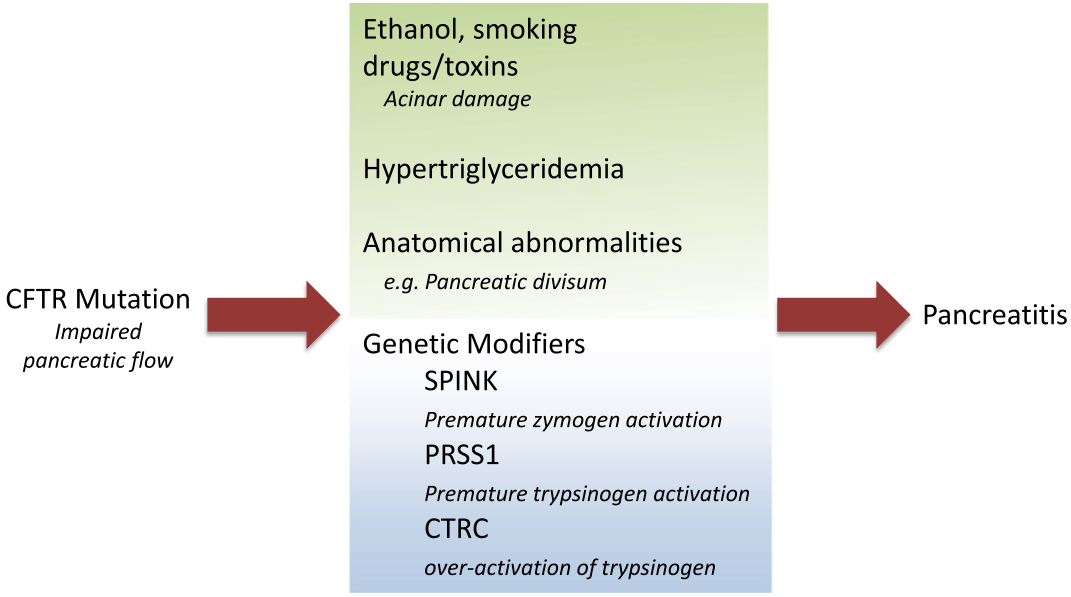


Fig. 3. CFTR mutation with non-CFTR modifiers in adults (green) and children (blue) that likely results in the development of pancreatitis in patients with CF (adapted from Assis and Freedman [70]).

CT imaging has similar sensitivity as standard MRI in adults, its use in children in discouraged due to radiation exposure [40,44].

Long-term management requires close consultation with a gastroenterologist to assist in determining appropriate medications (e.g. acid reduction, antioxidants, pancreatic enzymes, chronic pain medications) and potential role of endoscopy and/or surgical interventions. Including total pancreatectomy with islet autotransplantation (TPIAT). Reducing environmental factors such as smoking, alcohol and hypertriglyceridemia remain critical. Chronic pain may result in significant morbidity and is often very difficult to manage. Patients may benefit from support of a chronic pain specialist working in close collaboration with their gastroenterologist.

The use of a low-fat diet in the context of CF-associated pancreatitis is of unclear benefit and not advisable. In patients with CF and ARP the implementation of a low-fat diet is likely to have a profound negative influence on nutrition and nutrition-related pulmonary outcomes.

Patients with non-CF associated ARP or CP are at risk for developing Type 3c diabetes and/or PI [46], but this association has not been shown to be true in CF-related pancreatitis. CF-related diabetes (CFRD) is typically occurs with severe class I or II mutations, typically not associated with pancreatitis in CF patients, and occurs independent of PI status [47]. Routine screening for CFRD per current guidelines is sufficient and should not be altered due to ARP or CP [48].

Finally, CP is known to increase lifetime risk of developing pancreatic cancer [49]. Additionally, it is suspected that pancreatic cancer is more common in patients with CF than the general population [50,51]. CFTR mutations have been shown to be associated with an increased risk of pancreatic cancer (odd ratio 1.4) and younger age at time of pancreatic cancer diagnosis among non-CF patients [52,53]. Although specific screening guidelines for pancreatic cancer in CF do not exist, a high-index of suspicion should be maintained by the clinician in patients who present with unexplained abdominal pain, jaundice and/or nutritional decline.

## 4. Endpoints for future clinical trials

The era of CFTR potentiators and correctors has resulted in newfound optimism in the treatment of CF. The effects of these medication on pancreatic pathophysiology though remain to be seen. The in utero damage and chronic fibrocystic changes affecting the pancreas in the majority of CF patients suggests the new classes of medications may offer little benefit. Previous reports of improved weight gain and body mass index (BMI) have been largely theorized to be secondary to improved intestinal pH, decreased intestinal inflammation with improved absorption and normalization of intestinal histopathology changes [54–57]. However, recent findings in the ivacaftor trials have shown not only improved in patients' BMI z-scores, but also improved fecal elastase levels [58]. This data suggests that the new potentiators and correctors may have more benefit to pancreatic outcomes than previously considered.

In order to fully determine the utility of these medications on CF pancreas outcomes more will need be understood about the effect of these medications on the cellular level of the pancreas. Specifically the ability of these medications to restore both $Cl^-$ and $HCO_3^-$ flow as well as change the viscosity of pancreatic juice. Clinically though, outcomes such as the ability to wean PERT, incidence of pancreatitis, improved exocrine pancreatic function and nutritional parameters will need to be followed.

It is plausible that CFTR potentiators and correctors may have a therapeutic role in patients with ARP and CP who carry

at least one CFTR mutation but do not fulfill the criteria for CF. Future studies are necessary.

## 5. Pancreatic cystosis

### 5.1. Background and presentation

Small pancreatic cysts are relatively common among patients with CF, but cysts larger than 1 cm are less common, although may occur in ~8% of CF patients, and are termed pancreatic cystosis [59,60]. In pancreatic cystosis, the parenchyma of the pancreas is replaced by multiple cysts of various sizes and abnormal pancreatic tissue [61]. Patients tend to be asymptomatic and present during the second decade of life as an incidental finding on abdominal imaging, although vague complaints of abdominal pain, early satiety and/or nausea may be present [62]. The cyst(s) are usually discovered as an abdominal mass on physical exam or as part of routine abdominal imaging for abdominal pain (i.e. abdominal ultrasound) [63,64]. Symptoms are believed to occur secondary to mass-effect, vascular compromise or hemorrhage of the cyst [65].

The pathophysiology is believed to be secondary to decreased $HCO_3^-$ transport resulting in dehydrated pancreatic secretions with a high protein concentration. Ultimately this leads to inspissation of secretions, ductal ectasia, inflammation and eventual macrocyst formation, although why only select patients develop this manifestation is unclear. Correlation between CFTR mutation and pancreatic cystosis phenotype has not been formally evaluated. However, a review of the literature revealed 26 patients with confirmed pancreatic cystosis. Of these patients, with ages ranging from 9 to 19 years old, only 10 reported gender (7 males and 3 females) and of the six that mentioned CFTR mutations, each had at least one copy of p.F508del [60–64,66–69].

### 5.2. Management

Management is based purely on symptoms with cyst size exerting no influence on therapy. Although ultrasound is typically the initial imaging modality, MRI is the most accurate method of evaluating cyst and potential impact on adjacent anatomical structures [64]. If symptoms warrant intervention, either surgical intervention or endoscopic cyst gastrostomy are the only available surgical options. Recently available and future CFTR modulator therapies (e.g. Orkambi®) may have a potential role in lieu of surgical intervention, although no data exists at this time. We propose the following decision algorithm (see Fig. 4).

## 6. Future directions

Pancreatitis among patients with CF represents a significant source of morbidity. More effective methods to identify those patients with CF whom are at greatest risk for developing pancreatitis are needed, as are CF-specific therapeutic plans. The use of potentiators and correctors in CFTR-associated pancreatitis offers optimism but their in-vivo effectiveness has yet to be fully explored.

## 7. Clinical practice points

- ~20% of pancreatic sufficient patients with CF will develop pancreatitis
- The risk of developing pancreatitis in CF can be predicted using the pancreatic insufficiency prevalence (PIP) score

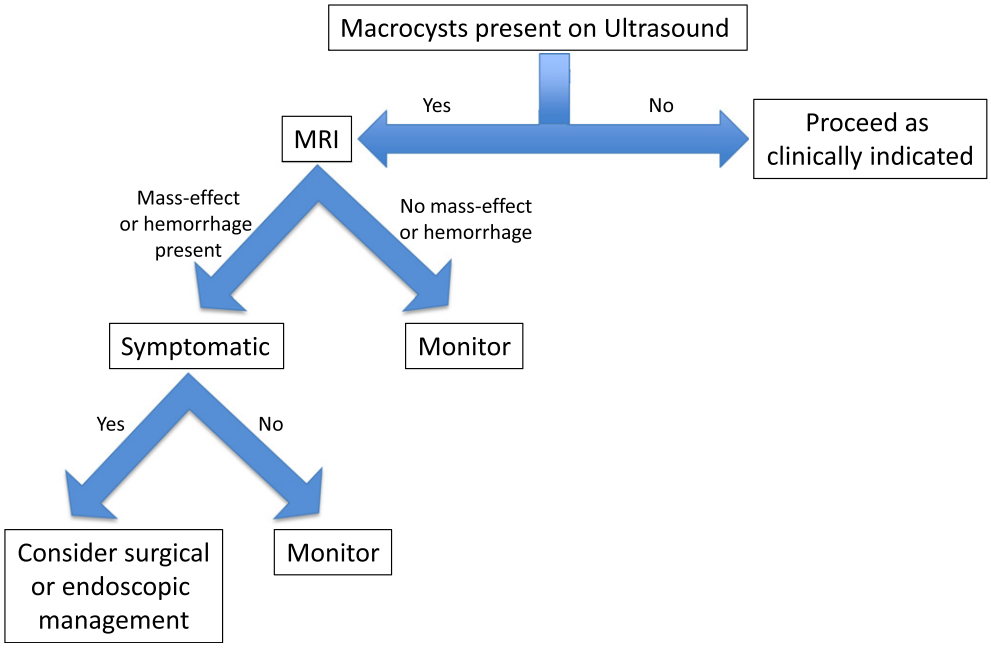


Fig. 4. Proposed decision making algorithm for pancreatic cystosis.

- Specific guidelines for CF associated pancreatitis do not yet exist; therefore, age-appropriate general pancreatitis management guidelines should be used as a general reference
- Pancreatic cystosis is a rare manifestation of CF and is typically identified as an incidental finding on abdominal imaging, however, symptoms may occur secondary to mass-effect, vascular compromise or hemorrhage of the cyst

## 8. Summary

Pancreatic sufficient CF patients are at risk for developing pancreatitis. Presentation of pancreatitis in patients with CF is no different than in the general population and should be considered in all pancreatic sufficient patients with unexplained abdominal pain and/or emesis. Therapy is no different than in the general population and any patient with ARP or CP should be referred to an experienced gastroenterologist. The effectiveness of potentiators and correctors on pancreatic manifestation of CF are yet to be determined.

## Conflict of interest

Authors declare no conflict of interest.

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