6.2.1 Exocrine pancreatic insufficiency

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1. INTRODUCTION

- Exocrine pancreatic insufficiency is a biological and clinical condition that is characterized by a progressive loss of pancreatic parenchyma. In CF, this loss is the result of defective CFTR function that leads to decreased transport of chloride and sodium into the pancreatic ducts. Pancreatic secretions become viscous and inspissated into the ducts resulting in their complete obstruction and upstream deleterious inflammatory and atrophic effects on the acinar cell mass.
- In the presence of *CFTR* variants causing severe CFTR dysfunction, pancreatic duct obstruction and acinar cell mass atrophy begin already during the mid-trimester of pregnancy. However overt pancreatic insufficiency will not appear until more than 90% of pancreatic function is lost.
- About 2/3 of infants with CF have pancreatic insufficiency at birth and almost 85% of patients will be affected by pancreatic insufficiency at some point in their lifetime.
- In their vast majority, patients with pancreatic insufficiency will not develop episodes of acute pancreatitis, however patients with pancreatic sufficiency may experience episodes of acute pancreatitis.

2. DIAGNOSTIC CRITERIA OF EXOCRINE PANCREATIC INSUFFICIENCY

- Measurement of serum amylase and lipase has **no role in the diagnosis of pancreatic insufficiency** because these enzymes are not correlated with the pancreatic ductular and acinar cell secretion and function.
- Pancreatic function tests (PFT) are either **direct** or **indirect** (**Table 1**).
  - The **direct PFT** represent the gold standard for the diagnosis of pancreatic insufficiency. They assess the secretion of bicarbonate-rich fluid from the pancreas within the duodenum. A peak of bicarbonate concentration of less than 80 mEq/L is consistent with the formal diagnosis of pancreatic insufficiency. However, this test is rarely used because it is cumbersome and expensive.
  - **Indirect PFT** are performed on stool samples to measure either the levels of the remaining pancreatic enzymes or the malabsorption that results from pancreatic function loss. They have the following advantages: cheap, rapid, single sampling of stools. The most commonly used test is the measurement of **fecal elastase**:
    - It is not affected by gastric resection, malabsorption due to intestinal disease, or alteration of the gastric motility.
    - It consists in an immunologic assay (sandwich ELISA) that quantifies the amount of the enzyme and not its activity that may be influenced by other factors.
    - It is usually stable over time (but it should be measured within 48 h and samples should be kept at 4°C) and it does not vary under physiological conditions, except in

cases of profuse diarrhea and villous atrophy. Therefore, **fecal elastase is usually measured on a spot sample**.

- **All patients with cystic fibrosis should be screened for pancreatic insufficiency using the fecal elastase test.**

Table 1 : Pancreatic Function Tests (PFT) to detect exocrine pancreatic insufficiency (PI)

Test	Usefulness	Performance	Remarks
Serum amylase and lipase	Not useful	Not sensitive	
Direct PFT	Gold standard	Sensitivity : 85-87%	Cumbersome, not used
Indirect PFT: Sudan staining	Not useful	Not specific	Obsolete
Indirect PFT: 72 hour steatorrhea	Gold standard	Sensitivity > 90%	PI if > 7g fat/day Cumbersome, rarely used
Indirect PFT: fecal elastase	Test of choice	Sensitivity > 90%	PI if < 200 μg/g

Abbreviations: PFT=pancreatic function tests, PI=pancreatic insufficiency

3. CLINICAL SYMPTOMS OF EXOCRINE PANCREATIC INSUFFICIENCY

- The symptoms may vary according to the amount of pancreatic loss and patient's age (**Table 2**).

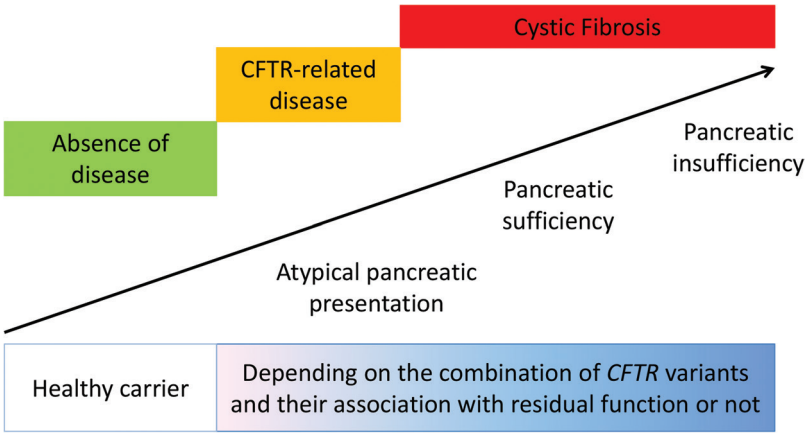
Table 2: Symptoms of exocrine pancreatic insufficiency

Bulky and oily stools
Abdominal distension
Failure to thrive/weight loss
Deficiency of fat soluble vitamins

4. GENOTYPE-PHENOTYPE CORRELATION

- *CFTR* genotype and CF phenotype associations are often discordant, and for that reason the genotype may not predict the clinical course of individual patients **(see also Chapter "*Pathogenesis*")**. The clinical phenotype (type and number of affected organs, severity of the disease, age of onset) depends on genetic and environmental factors.
- The spectrum of exocrine pancreatic function disturbances in CF and CFTR-related disease is shown in **Figure 1.**
- CF variants such as R117H and R334W are associated with pancreatic sufficiency whereas F508del, I507del and Q493X variants are always associated with exocrine pancreatic insufficiency.

Figure 1: Spectrum of exocrine pancreatic function disturbances in CF and CFTR-related disease



5. PANCREATIC ENZYME REPLACEMENT THERAPY (PERT)

- The main goal of PERT is to provide sufficient amount of pancreatic enzymes (mainly lipase) to ensure either a normal growth in infancy and/or a stable body weight over time.
- Several formulations do exist in the market, all of which contain various amounts of lipase, protease and amylase **(see also Chapter "*Nutrition*")**. Of note, units of activity may vary by country.
- In CF patients with pancreatic insufficiency, we are mainly interested in lipase supple-mentation. Creon® contains the highe**st** amount of lipase.
- About 2'000 lipase units will digest 1 g of fat. In adults, a cumulative quantity of 25'000 to 40'000 units of lipase need to enter the duodenum with postprandial chime to provide an effective digestion. To have a better effect of the enzymes, they should be taken in the middle and at the end of the meal.
- PERT endpoints (**Figure 2**) are fulfilled in the presence of decreased stool frequency and improved stool consistency. As shown in Figure 2, a proton pump inhibitor may be used to increase the duodenal availability of active lipase by increasing the luminal pH.
- The control of pancreatic insufficiency symptoms should guide the dosing of pancreatic enzymes. High doses of pancreatic enzyme replacement therapy have been associated with the development of fibrosing colonopathy. Caution should be exercised not to exceed the maximal doses of 2'500 lipase units/kg of body weight per meal or 10,000 lipase units/kg of body weight per day.
- Drugs used for PERT are shown in **Table 3**.

Figure 2: **Details of PERT in a daily practice.**

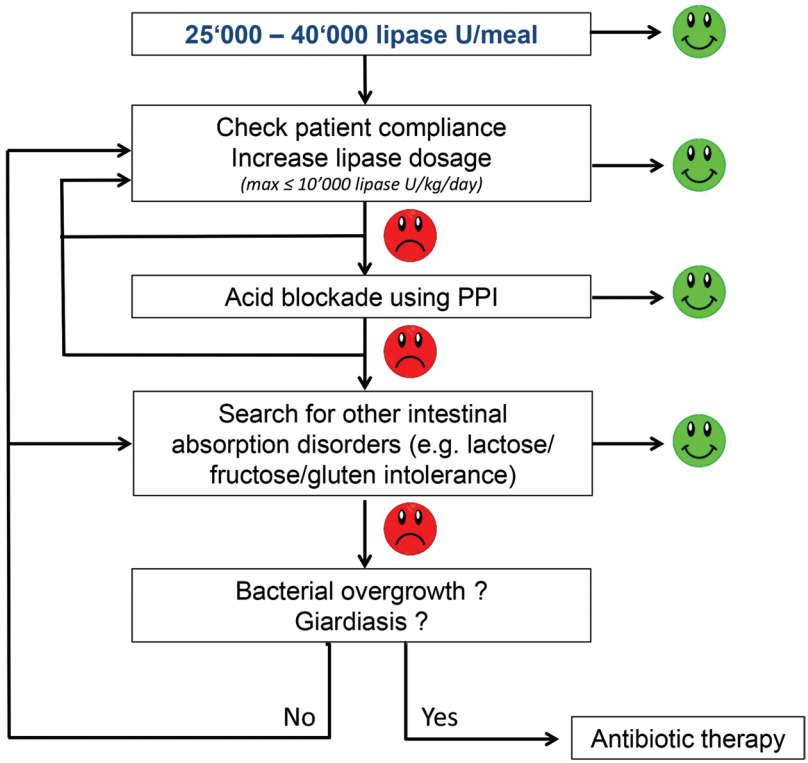


Table 3: Drugs used for PERT

Drug	Lipase (U)*[a]	Protease (U)*[a]	Amylase (U)*[a]
Creon® 10’000	10’000	600	8’000
Creon® 25’000	25’000	1’000	18’000
Creon® 40’000	40’000	1’600	25’000
Panzytrat® 10’000	10’000	500	9’000
Panzytrat® 25’000	25’000	800	12’000
Pertzye® 8’000*[b] (not available in Switzerland)	8’000	460	7’290
Pertzye® 16’000*[b] (not available in Switzerland)	16’000	920	14’580

*[a] Enzyme content is expressed in European Pharmacopoeia (PhEur) units[7]
*[b] Pertzye®, but also Ultresa® and Viokace® are preparations of pancreatic enzymes approved by the FDA which contain much higher concentrations of protease and amylase. Some CF patients may benefit of these preparations when usual preparations available in Switzerland are not sufficient.

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6.2.2 Pancreatitis

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1. INTRODUCTION

- **Acute pancreatitis** is an inflammatory condition that usually occurs in an otherwise healthy pancreatic parenchyma. It is an isolated phenomenon, in most cases characterized by sudden epigastric pain associated with a concomitant rise of serum lipase. A few weeks after the attack has occurred, the parenchyma will fully recover.
- **Chronic pancreatitis** is an acute episode of pancreatitis that occurs in an already damaged parenchyma.
- **Acute recurrent pancreatitis** is an acute disease that eventually evolves to chronic pancreatitis due to progressive duct obstruction, as observed in cystic fibrosis.
- Upon admission of a patient, it is difficult to distinguish between an episode of isolated acute pancreatitis and the first attack of either recurrent pancreatitis or chronic pancreatitis. Only the follow up will help differentiate these clinical conditions.
- In western countries, most acute pancreatitis cases are associated with either common bile duct (CBD) stone migration or alcohol addiction, both of which may occur in CF patients. Risk factors for CBD stones are presented in **Table 1**.

Table 1: Risk factors for common biliary duct stones

Age
Female sex
Cholecystectomy
Pregnancy and estrogen therapy
Rapid weight loss
Diabetes
Ileal resection
Drugs such ceftriaxone, sandostatine

2. PANCREATITIS IN CF

2.1 Epidemiology

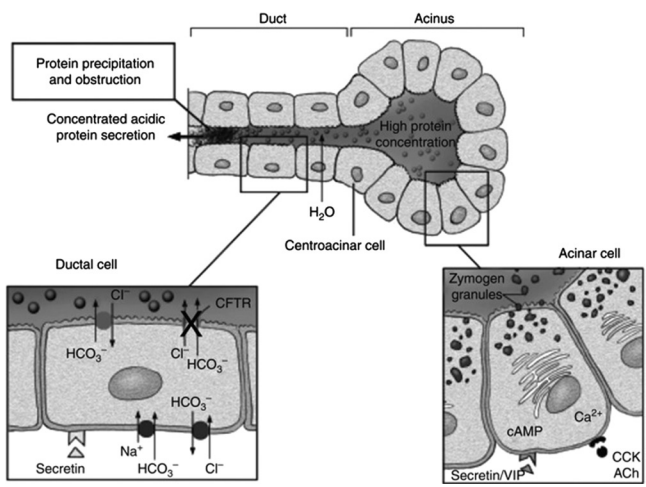
- In a large cohort, it was found that **pancreatitis occurs only in pancreatic sufficient (PS) CF patients**. Why pancreatitis arises only in a minority of these subjects is unclear but data suggest pancreatitis is mostly associated to *CFTR* variants having some residual function, such as class IV and V variants.
- About 10–17% of PS CF patients may develop acute pancreatitis during childhood or early adulthood (incidence about 1.7%). Very rarely acute pancreatitis may be the first recognized symptom of CF**.**

- **Pancreatitis may also be a phenotype of CFTR-related disease (see Chapter *"Diagnosis in adults"*)**.
  - About 30-40% of "non-CF" patients suffering from idiopathic acute or chronic pancreatitis carry at least one *CFTR* variant. About 18% of them carry one CF-causing variant which is associated to a 6.3 times greater risk of idiopathic pancreatitis. This risk increases further (to 37 times) in patients with a residual function *CFTR*-variant on the other allele.
  - Carrying both *CFTR* and *SPINK1* (serine peptidase inhibitor Kazal type 1) variants strongly increases the risk of idiopathic pancreatitis.

2.2 Mechanisms

- Reduction or absence of CFTR function is responsible for decreased transport of Cl^- and HCO_3^- in the lumen of pancreatic ducts. As a result, pancreatic fluid in the ducts is too concentrated and tends to precipitate because proteins, including digestive enzymes, are insufficiently soluble in acidic conditions **(Figure 1)**.
- The risk of pancreatitis increases when functional acinar tissue is sufficient and ductal obstruction is significant. In severe CFTR impairment, ductal obstruction is more pronounced but acinar function is absent resulting in almost no risk of pancreatitis.
- Acidification of the ductal lumen seems to impair tight junctions allowing zymogens to reach the interstitial fluid and then to be activated. Ultimately, these events lead to tissue inflammation, collagen production, fibrosis and finally to exocrine pancreatic insufficiency.

Figure 1: Mechanisms of pancreatitis in CF. Lack of CFTR leads to decreased production of Cl^- and HCO_3^- and consequently precipitation of proteins into the pancreatic ductal lumen (Reprinted with permission from Wilschanski M, Durie PR. Patterns of GI disease in adulthood associated with mutations in the CFTR gene. Gut 2007;56:1153-63[1].)



- This process starts *in utero* already and, at birth, it is associated with increased release of pancreatic proteins, such as immune reactive trypsinogen (IRT), in the blood. IRT level is the first test used by most neonatal screening programs.

3. ACUTE PANCREATITIS AND ACUTE RECURRENT PANCREATITIS

3.1 Diagnosis

- Acute pancreatitis is characterized by acute and sudden epigastric pain (reaching its maximum within 15 min) **(Table 2)** associated with increased serum levels of pancreatic enzymes at least 3 times the normal value **(Table 3)**.
- The pain may last for hours up to 2-3 days. It is sudden when stones spontaneously migrate into the CBD whereas its installation is typically slower in CF.
- Imaging studies are not needed to confirm the initial diagnosis, unless other diseases are clinically suspected (e.g. perforation, bowel obstruction etc).
  - Chest radiography may help to identify the presence of pleural effusion.
  - Abdominal ultrasound can assess the presence of biliary duct dilation, an indirect sign of CBD stones or obstruction.
  - CT scan performed after day 3 may evaluate the presence and/or extent of pancreatic acute fluid collection and necrosis.
  - Cholangio-MRI has no role upon admission but may be used subsequently to identify any ductular abnormality such as stenosis that could be ultimately treated endoscopically.
- **The final diagnosis of acute pancreatitis is confirmed in the presence of two of the following: 1) sudden abdominal pain, 2) serum lipase > 3X upper limit of normal (ULN), 3) pancreatitis signs on imaging modalities.**

Table 2: Frequency of symptoms and signs of acute pancreatitis

Pain	> 90%
Nausea	> 90%
Vomiting	> 90%
Back radiation	50%
Painless disease	5-10%
ALAT > 3 x ULN (sign of common bile duct migration)	95%

Table 3: Laboratory diagnostic criteria of acute pancreatitis

	Sensitivity	**Specificity**
Serum amylase > 3 x ULN	69-83%	85-95%
Serum lipase > 3 x ULN	87-99%	95-100%

3.2 Identification of causal factors

- Although, pancreatitis is due to intra-pancreatic obstruction in CF, other or associated causes should be considered depending on history and clinical findings **(Table 4)**.
- **A biliary origin of acute pancreatitis must be ruled out** in each episode because re-currence may happen if stones remain in place.

Table 4: Causes of acute pancreatitis

Pathological mechanism	Frequency	Type of disease
Obstructive	45%	Stone
		Intraductal Papillary Mucinous Neoplasia
		Ampulloma, metastasis
		Oddi dysfunction
Toxic	40%	Alcohol
		Snake venom, scorpion venom
Drug	2%	>200 compounds
Metabolic	< 1%	Hypercalcemia
	1.3%	Hypertriglyceridemia
Infection	Rare	Viruses, parasites
Genetic	Rare	Association with PRSS-1, SPINK-1 mutations
Other	Rare	Auto-immune pancreatitis

3.3 Prediction and characterization of severity

- The severity of pancreatitis is mainly associated with the presence of necrosis and its extent. Acute pancreatitis is mild in 80% of cases, moderately severe in 15% and very severe in <5%.
- Many scores have been and are still being used to predict the severity of an episode of pancreatitis but none of them is sufficiently reliable.
  - **CRP levels > 150 mg/dl within 48 hours upon admission seem to be the most powerful predictor of severe pancreatitis** and should be used in daily practice.
  - Prediction of severe disease could also be performed using the APACHE II system (with a cutoff of ≥8) when the patient is admitted in intensive care unit (ICU).
  - Ranson score is scarcely used because it is imperfect.
- The severity of acute pancreatitis is based on clinical signs, biological parameters and imaging studies. A CT index score has been developed based upon the degree of necrosis, inflammation, and the presence of fluid collections.

- Acute pancreatitis is therefore characterized as:
  - **mild** when there is no organ failure or local complications.
  - **moderately severe** in the presence of transient organ failure or local complications (resolution within 48 hours).
  - **severe** in the presence of organ failure and local complications that are prolonged for more than 48 hours.
- Pancreatic sufficient CF patients rarely suffer from severe pancreatitis.
- **Table 5** depicts the revised Atlanta Criteria used for the classification of acute pancreatitis and its complications.

Table 5: Atlanta Criteria for the classification of acute pancreatitis and its complications

1. Intersitial edematous pancreatitis	Inflammation without necrosis
2. Necrotizing pancreatitis	Inflammation with pancreatic and or peri-pancreatic necrosis
3. Acute peripancreatic fluid collection	Peripancreatic fluid associated with interstitial pancreatitis
4. Pancreatic pseudocyst	Encapsulated collection of fluid
5. Acute necrotic collection	Collection with variable amount of fluid and necrosis
6. Walled-off necrosis	Encapsulated collection of pancreatic/peri-pancreatic necrosis

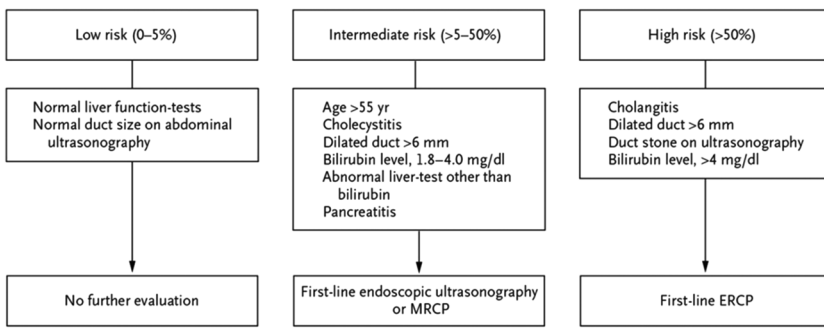
3.4 Management

- Currently, there are no CF-specific recommendations for the management of pancreatitis.
- Patients with predicted severe pancreatitis should be admitted in the ICU.
- **Adequate hydration** with normal saline or lactated Ringer's is mandatory to decrease the risk of acute tubular necrosis and necrotizing pancreatitis. Regular monitoring of vital and biological (hematocrit, blood urea nitrogen, CRP) signs are used to adapt fluid rate.
- **Control of abdominal pain** is often challenging:
  - Analgesics: paracetamol and NSAID are usually the first choice agents.
  - In case of insufficient response, weak opioids such as tramadol should be added.
  - For severe pain, opioids should be considered but there is an ample debate on the best choice for pain relief: pethidine (bolus 25 to 100 mg SC or IM; 25-50 mg IV) or fentanyl (bolus 25 to 75 μg IV), which has a good safety profile, or even morphine. Because respiratory depression is a common side effect of opioids, respiratory parameters should be carefully monitored in CF patients.
- **Nutrition:**
  - Controversy exists around the use of pancreatic enzymes during acute pancreatitis. They may be tried and continued if they allow pain reduction.

- In non severe pancreatitis, no specific dietary measures are proposed but rather a progressive and early enteral nutrition based on clinical symptoms and when the pain has decreased (usually 24-48h). It is well known that bacterial translocation from the gut may occur and cause infected pancreatic necrosis. Early enteral nutrition can reverse bacteria translocation and may help decrease morbidity and mortality rates of severe acute pancreatitis.
- Early enteral nutrition either through the naso-duodenal or naso-gastric route should be undertaken as quickly as possible in case of severe pancreatitis, to decrease the morbidity and mortality rate. Because of strong metabolic stress, caloric needs may reach 140% of basal needs (30-35 kcal/kg/day). The choice of nutritional supplements should be discussed with dieticians.

- As stated earlier, a biliary origin of acute pancreatitis must be ruled out in each patient. The presence of CBD stones should be managed according to the established guidelines **(Figure 2)**. Endoscopic sphincterotomy is the method of choice to remove stones located in the common bile duct.
- Although early mortality (1st week) is a rare event associated with SIRS (Systemic Inflammatory Response Syndrome), late mortality of acute pancreatitis is due to infected pancreatic necrosis. The latter is caused by increased gut permeability and bacterial translocation into non viable tissue. This specific event occurs during the 2nd or 3rd week after admission. It is therefore pivotal to rule out such an event in severe acute pancreatitis and to perform a CT guided aspiration.

Figure 2: Management of common bile duct stones [reprinted with permission from Frossard JL et al. ERCP for gallstone pancreatitis. N Engl J Med 2014;370: 1954-5. Copyright ©Massachussetts Medical Society]



3.5 Prevention of recurrent episodes

- I*n vitro* and *in vivo* studies suggest that ethanol and fatty acids decrease *CFTR* expression and activity in the pancreatic ducts and increase further the risk of pancreatitis. Alcohol and cigarette consumption should be avoided to prevent recurrent pancreatitis.
- Low-fat diet to prevent chronic pancreatitis is currently not recommended in CF.

- Apart from management of CBD stones, no other specific preventive measures are recommended.
- If pancreatico-duodenal derivation is considered, it should be discussed with the gastro-enterology specialist.

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