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**).

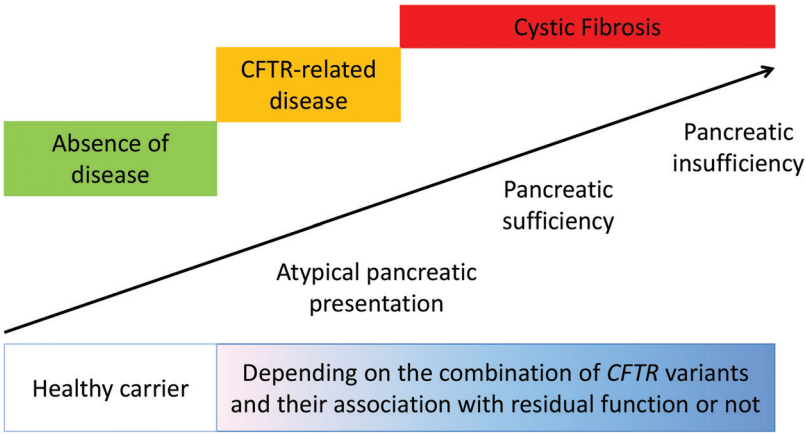
Table 2: Symptoms of exocrine pancreatic insufficiency

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.**

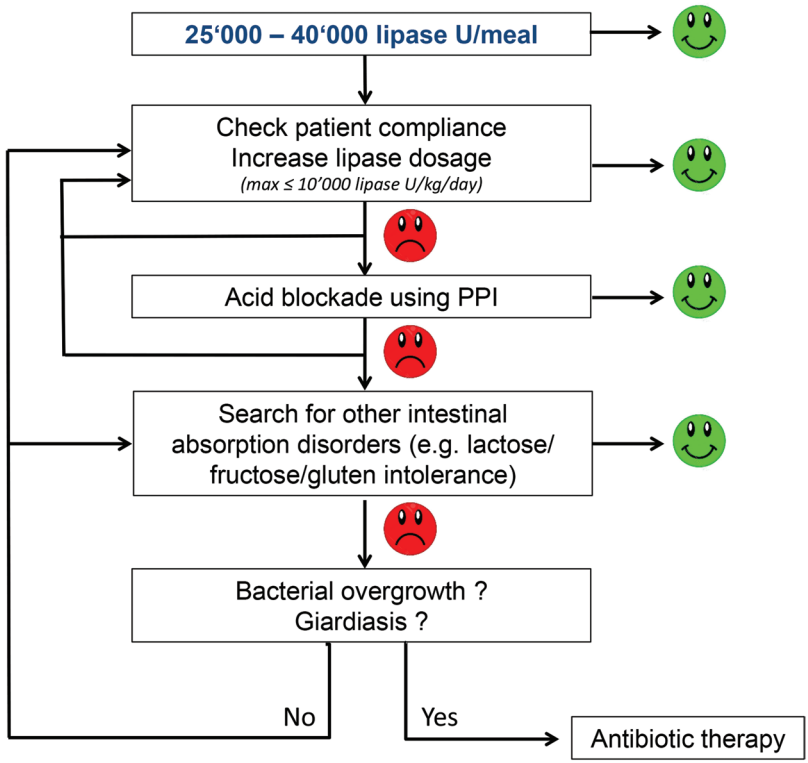


Table 3: Drugs used for PERT

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.

6. REFERENCES

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