CHAPTER 10 PANCREATIC ENZYME REPLACEMENT THERAPY

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Pancreatic insufficiency affects 90% of the CF population [478] and refers to the significantly impaired ability of the pancreas to secrete sufficient enzymes such as lipases, proteases and amylases needed for the normal digestion of fats, proteins and carbohydrates respectively [479]. In pancreatic insufficiency, >98% of enzyme secretory capacity is lost and manifestations of maldigestion such as steatorrhoea are evident [231].

Individuals with pancreatic insufficiency require pancreatic enzyme replacement therapy (PERT) to assist fat digestion and absorption. PERT refers to gelatin capsules filled with mini-microspheres or micro-tablets of lipase, amylase and protease, usually of porcine origin. Although amylase and protease secretion from the pancreas are also affected in pancreatic insufficiency, lipase is more rapidly denatured by other proteases in the duodenum [480] and so is contained in larger amounts in PERT preparations. Fat absorption in pancreatic insufficiency is therefore much more affected than carbohydrate and protein absorption and so PERT is dosed based on the fat content of foods.
Pancrelipase brands and preparations available in Australia and New Zealand (NZ) include:

- **Creon®** (pancrelipase) – enteric coated mini-microspheres which are similar in size to food particles
  - Creon 10 000, 25 000 and 40 000 – mini-microspheres encapsulated in a gelatin capsule
  - Creon Micro (used in infants) – mini-microspheres measured and dosed using a scoop
- **Panzytrat®** 25 000 (pancrelipase) – enteric coated micro-tablets of uniform size

The above preparations all contain a combination of porcine-derived lipases, proteases, and amylases, concentrated as pancrelipase. Refer to table 10a for more information regarding the preparations and composition of available PERT in Australia and New Zealand.

Table 10a. Composition* and availability of pancrelipase preparations available in Australia and NZ

	Creon Micro® per scoop	Creon 10 000® per capsule	Creon 25 000® per capsule	Creon 40 000® per capsule	Panzytrat® per capsule
Lipase (BP units)	5000	10 000	25 000	40 000	25 000
Amylase (BP units)	3600	8000	18 000	25 000	22 500
Protease (Ph. Eur. Units)	200	600	1000	1600	1250
Granule size (diameter mm)	0.7 - 1	0.7 - 1.6	0.7 - 1.6	0.7 - 1.6	2
Available in New Zealand**	×	✓	✓	×	✓
Available in Australia**	✓	✓	✓	✓	✓

**Measured PERT activities are generally higher than the declared activities to ensure the required minimum activity at the end of shelf life*
*** At time of publication*

Novel non-porcine PERT preparations have undergone and continue to undergo investigation for use in CF in the US [125,481]. They are a proprietary biotechnology-derived formulation of cross linked lipase, protease and amylase and are stable in an acidic pH for reliable activity in the proximal small intestine. A novel device, Relizorb®, which contains lipase that digests fat as the enteral feed passes through the cartridge, has recently become available in the US. Non-enteric coated PERT preparations are not available in Australia or NZ.

The mechanism of PERT activation is outlined in figure 10a.

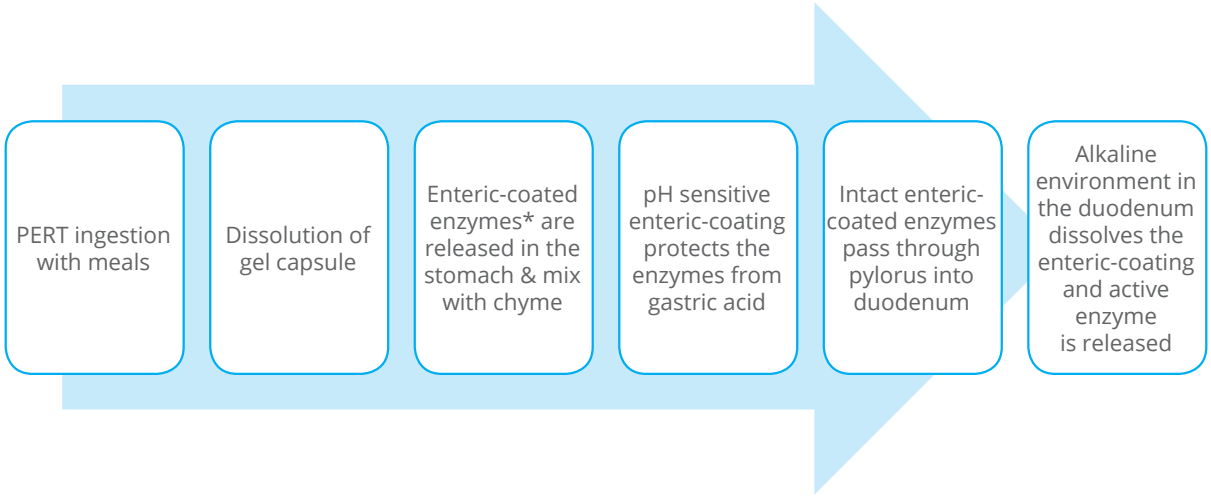

Figure 10a. Pancreatic Enzyme Replacement Therapy activation mechanism [482]

** Enteric-coated enzymes refers to the enteric coated mini-microspheres and micro-tablets*

PERT is usually administered orally with fat containing food and fluid with the aim of arriving in the duodenum simultaneously with the food or fluid. Once activated, lipase hydrolyses fats into glycerol and fatty acids ready for absorption. The ultimate goal of PERT treatment is to optimise nutrient digestion and absorption and in turn achieve optimal growth and nutritional status [483].

Disease Aetiology

PANCREATIC INSUFFICIENCY

The primary defect in CF, a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, leads to impaired chloride secretion, inhibition of bicarbonate uptake and impaired luminal bicarbonate secretion. This results in the contents of the pancreatic ducts becoming dehydrated, leading to inflammation and scarring of the acinar tissue [484]. In addition, the thick viscous secretions produced obstruct the pancreatic ducts, leading to fibrosis and impaired pancreatic enzyme secretion into the intestinal lumen. Individuals with pancreatic insufficiency require PERT to assist fat digestion and absorption.

The pancreas has a high reserve capacity and compensatory mechanisms, with clinical symptoms of insufficiency usually only manifesting when >98% of enzyme secretory capacity is lost [231]. The most severe clinical consequence of pancreatic insufficiency is steatorrhoea, characterised by fatty, frothy, offensive smelling and buoyant stools. Fat maldigestion and malabsorption can lead to fat soluble vitamin deficiencies [485], growth failure and malnutrition [486].

There are known genotype-phenotype correlations that influence pancreatic function in CF, with most individuals with a severe mutation on both alleles expressing a pancreatic insufficient phenotype [487]. Some individuals may be pancreatic sufficient at birth and develop pancreatic insufficiency in the first few years of life [488] with one study finding 21% of patients who were pancreatic sufficient at birth had developed insufficiency between 3-36 months of age [489]. These individuals are more likely to have a genotype that confers pancreatic insufficiency [490].

PANCREATIC SUFFICIENCY

A small percentage of people with CF are classified as pancreatic sufficient. These individuals usually carry a mild mutation on one or both alleles. Although these patients are deemed pancreatic sufficient, pancreatic function is not entirely normal [231]. A wide range of pancreatic function is observed in pancreatic sufficient individuals with CF, however secretory capacity is not impaired to the point that steatorrhoea becomes evident. Some individuals with pancreatic sufficiency are at risk of progressing to pancreatic insufficiency, particularly after the development of recurrent episodes of pancreatitis [232].

ACUTE PANCREATITIS

Acute pancreatitis is a known but uncommon manifestation of CF and is characterised by abdominal pain associated with inflammation and swelling of the pancreas. The presence of acinar tissue is necessary for pancreatitis to occur and it therefore rarely occurs in individuals with pancreatic insufficiency, while individuals with pancreatic sufficiency have been reported to have a 22% risk of developing pancreatitis in their lifetime [232]. Moreover, patients with

pancreatic sufficiency and CFTR genotypes associated with mild disease phenotypes have a greater risk of developing pancreatitis than patients with pancreatic sufficiency and genotypes associated with moderate to severe disease phenotypes. With sufficient tissue destruction in pancreatitis, progressive loss of pancreatic acinar tissue function can lead to insufficiency over time [491].

Assessment

Assessment to determine pancreatic insufficiency should be coordinated by or managed in conjunction with a specialist CF gastroenterologist. In centres where a specialist CF gastroenterologist is not available, advice should be sought from a major CF centre for areas of uncertainty. For people with confirmed insufficiency, assessment should focus on adequacy of PERT dosing and administration.

DIET

For people with CF and confirmed pancreatic insufficiency, the following should be considered in relation to PERT when conducting a dietary assessment:

- Dosing - amount of PERT taken with each meal and snack, focusing on fat containing foods
- Adherence - particularly at school for the paediatric CF population
- Timing of PERT in relation to food and fluids
- Physical storage of PERT

CLINICAL

Key points to consider as part of a clinical assessment when pancreatic insufficiency is suspected include:

GENOTYPE

- People with a class I-III mutation on both alleles are more likely to be pancreatic insufficient [232].
    - If confirmed pancreatic sufficient at diagnosis, people with a class I-III mutation are more likely to develop pancreatic insufficiency within the first few years of life [488,489].
- The Pancreatic Insufficiency Prevalence score is a recently developed novel and validated classification system for mutation severity that can be used to quantitatively determine the likelihood of a patient having pancreatic insufficiency [232,492].

SIGNS AND SYMPTOMS

- Poor weight gain and/or weight loss in conjunction with abdominal pain, abdominal distention, gas, frequent stooling and steatorrhoea (frothy, oily, offensive smelling and buoyant stools) may indicate pancreatic insufficiency [478]. These signs and symptoms should also be considered when assessing PERT adequacy and efficacy.
- Small intestinal confounding factors (e.g. bicarbonate deficiency, small bowel bacterial overgrowth, bile-salt deficiency and non-CF enteropathies such as coeliac disease) may present with similar signs and symptoms to pancreatic insufficiency and should also be considered.

For people with CF and confirmed pancreatic insufficiency, gastric emptying should also be considered as part of a clinical assessment.

- Fast gastric emptying can overwhelm the functional capacity of the intestine causing malabsorption and diarrhoea [493,494].
- Delayed gastric emptying can induce satiety and inhibit further intake [493].

Does gastric emptying rate impact PERT efficacy in people with CF? PICO10.1.1

[Grade C] Gastric emptying rate may impact PERT efficacy and should be considered in people with CF. [111,112]

Studies of gastric emptying in CF have found conflicting results of accelerated [495], normal [496] and delayed [497] solid or liquid gastric emptying in CF. Although the studies to date have been small and limited to the paediatric population, one study suggests that people with CF who experience fast gastric emptying may benefit from taking PERT before a meal [112], rather than during or after.

BIOCHEMICAL & LABORATORY DATA

It is recommended that all people with CF undergo formal testing to determine pancreatic status on diagnosis. Individuals who are deemed pancreatic sufficient at diagnosis who later display signs and symptoms of fat malabsorption should undergo re-testing for pancreatic insufficiency, particularly those with two gene mutations known to be associated with pancreatic insufficiency. It has been suggested that re-testing for pancreatic insufficiency occur annually for this population group [78]. There is not universal consensus on a single test to use to determine pancreatic status. It is suggested that local guidelines are used to inform which test to use to diagnose pancreatic insufficiency and to inform frequency of screening for pancreatic insufficiency in the pancreatic sufficient CF population.

Exocrine pancreatic function is notoriously difficult to assess as the pancreas and its secretions are relatively inaccessible. A number of direct and indirect tests available to diagnose pancreatic insufficiency have been described and are listed below. More detailed descriptions of these and other tests are described in the *Australasian guidelines for the management of pancreatic exocrine insufficiency* [498].

It is important to note that direct tests are rarely used in clinical practice due to their invasive nature. Indirect tests, particularly the simple faecal elastase test, are most often used in clinical practice despite their limitations, due to being more widely available and relatively non-invasive in nature.

All tests should be interpreted in conjunction with a specialist CF gastroenterologist, and should consider the wider clinical picture including class of mutation, as well as the sensitivity and specificity of tests used. In centres where a specialist CF gastroenterologist is not available, advice should be sought from a major CF centre for areas of uncertainty.

ASSESSMENT OF PANCREATIC FUNCTION

DIRECT TESTS

Direct tests to determine exocrine pancreatic function require duodenal intubation and collection of pancreatic secretions while the pancreas is stimulated with hormones such as secretin and cholecystokinin. The secretions are sampled to determine bicarbonate and enzyme outputs. This is then compared to normal values to determine level of dysfunction.

Secretin-cholecystokinin test

- Involves pancreatic stimulation with both secretin and cholecystokinin hormones, allowing for the simultaneous assessment of ductal and acinar secretory capacity and quantification of bicarbonate and enzyme outputs [499]
- Gold standard direct test of exocrine pancreatic function but impractical for routine clinical use
- Limitations include the invasive nature of the test (anaesthesia required) and cost

Endoscopic pancreatic function test

- Uses secretin only
- Shorter pancreatic secretion collection times
- Becoming an increasingly popular method to determine pancreatic function
- Use has been criticized as the test determines only ductal function and not acinar function, and shorter sampling times can overestimate pancreatic secretory capacity, leading to an incorrect diagnosis of pancreatic function [500]

INDIRECT TESTS

The most common indirect tests to determine exocrine pancreatic function are faecal or oral tests. These tests are cheaper and easier to administer and therefore are more widely used. There are also blood tests that can be used. Some of these tests can also be used to determine PERT efficacy.
Limitations of indirect tests include:

- Less sensitive and specific than direct tests
- Faecal tests detect abnormalities that occur as a result of pancreatic dysfunction rather than the dysfunction itself

The most common indirect tests are described below and summarised in table 10b.

FAECAL TESTS

Faecal Fat Balance (FFB) – 3 day faecal fat balance test

- Considered the gold standard for diagnosing and quantifying steatorrhoea [501]
- Has been used in the past to both diagnose pancreatic insufficiency and to determine adequacy of PERT
- The test involves:
  - Consumption of a high fat diet (100g fat) for 3-5 days
  - Quantification of mean daily fat intake via a weighed food intake record
  - Collection of stools (72hrs) and coefficient of fat absorption (CFA) determined
- Steatorrhea occurs when:
  - >7% of ingested fat is excreted in the stools in patients over 6 months of age [502]
  - >15% of ingested fat is excreted in the stools in patients under 6 months of age [503]
- Declined in popularity due to its limitations
  - Inconvenient for families with potential for poor adherence
  - Cumbersome and unpleasant for laboratory staff
  - Does not distinguish between pancreatic and non-pancreatic causes of fat malabsorption [504]
  - Has a low sensitivity (41.7%) for diagnosing pancreatic steatorrhoea [504]

Faecal Elastase-1 test

- Involves the enzymatic quantification of elastase in the stool
  - Faecal elastase is a pancreatic-specific protease that unlike chymotrypsin is not degraded by intestinal passage
- Highly sensitive (96%) and specific (100%) [505]
  - Faecal elastase of <100ug/g is highly predictive of pancreatic insufficiency
- Advantages
  - Only requires a single stool sample
  - Less cumbersome and unpleasant for both families and laboratory staff
  - Not affected by PERT and therefore can be useful for establishing pancreatic status in people who have already commenced PERT
- Limitation
  - False positive results can occur with non-pancreatic diarrhoea due to dilution [506]
  - Not useful for determining efficacy of PERT

Faecal chymotrypsin test

This test is no longer used to diagnose pancreatic insufficiency as the faecal elastase-1 test has been shown to have a higher sensitivity [507].

- Based on the enzymatic quantification of chymotrypsin in a small stool sample [508]

- Simple and easy to apply in clinical practice
- Limitations
    - Chymotrypsin is variably inactivated during the intestinal passage and the faecal chymotrypsin activity does not accurately reflect pancreatic secretion of the enzyme [509]
    - PERT should be ceased prior to testing as orally administered PERT can interfere with the determination of chymotrypsin in the stool

Microscopic assessment of stools for fat globules (e.g. Sudan III test)

- Involves staining a sample of stool and observing for neutral fat globules
- Less cumbersome than the faecal fat balance test
- Variability in performance and interpretation limits the overall sensitivity and reliability of the tests
- Suggested that these tests be used to screen for malabsorption. If fat globules are present, additional tests such as the FFB test may be performed [498]

Acid Steatocrit

- Determines the amount of fat in a single stool sample
- Faecal sample is homogenised and centrifuged for 15 minutes and the lipid is separated out [510]
- Lipid phase <10% of the total volumes is considered normal in people over 6 months of age
- Correlates well with the 3 day FFB test [511]

ORAL BREATH TESTS

Several substrates, most commonly ^{13}Carbon labelled, have been used to indirectly evaluate exocrine pancreatic function using a breath test [512,513].

- Involves the labelled substrate being given orally in a test meal
- Hydrolysis of ^{13}C-labelled substrate occurs in the small intestine by pancreatic lipase. The ^{13}C-labelled metabolites are then released, absorbed from the gut and metabolised in the liver. After hepatic metabolism, $^{13}CO_2$ is released in expired breath, which is captured at 15-30 minutes intervals over 6 hours.
- High sensitivity and specificity [513]
- Limitations
    - Expensive, time consuming and not widely available test
    - The test is an indicator of fat maldigestion only and is unable to differentiate between pancreatic and non-pancreatic causes

BLOOD TESTS

Serum trypsinogen test

- Measures the amount of trypsinogen in the blood
    - Trypsin is a protease secreted by the pancreas and released into the blood as the proenzyme trypsinogen
- Sensitive and non-invasive method that can be used to screen for pancreatic insufficiency in older children
- Validated in CF with levels below 20ng/ml indicative of pancreatic insufficiency in children over 7 years of age [514]
- Limitation
    - Serum trypsinogen levels fluctuate significantly in the first decade of life and so the test is not recommended to determine pancreatic insufficiency in children <7 years of age

Table 10b. Characteristics of selected indirect methods to determine pancreatic insufficiency and/or pancreatic enzyme replacement therapy adequacy

Test	Method	Strengths	Limitations	Determines pancreatic insufficiency	Determines adequacy of PERT
Faecal Fat Balance	High fat diet eaten and stools captured for 72 hours and then analysed for fat content.	'Gold standard' when performed accurately Indication of total fat absorption. High specificity (92%).	Invasive. Labour intensive. Expensive. Poor adherence. Does not distinguish between pancreatic & non pancreatic fat malabsorption. Low sensitivity for pancreatic fat malabsorption (42%).	✓	✓
Faecal Elastase	Quantification of elastase enzyme in the stool.	Only 1 stool sample needed. Not affected by dietary fat intake Can be completed on PERT. Highly sensitive (96%) and specific (100%) for pancreatic insufficiency in CF.	False positive results can occur due to diarrhoea.	✓	×
Faecal Chymotrypsin	Quantification of chymotrypsin enzyme in the stool.	Simple	Lower sensitivity than faecal elastase. High day-to-day variations. Must be off PERT.	✓	×
Acid Steatocrit	Faecal homogenate samples micro-centrifuged and steatocrit levels determined.	Lower cost than FFB Sensitive – 100% Specific – 95%	Invasive	✓	✓
Breath tests	Labelled substrate is ingested, oxidised and expired as CO_2 indicating lipase activity.	Non-invasive Simple to administer Sensitive- 89% Specific- 81% Reproducible	Expensive Gives indirect indicator of lipase activity rather than total fat absorbed.	✓	✓

Intervention

In people with CF presenting with poor growth and/or malnutrition and frequent bowel actions on diagnosis, PERT can be initiated prior to formal tests being conducted, particularly in individuals with two gene mutations known to affect pancreatic insufficiency. It is important, however, that formal testing occurs as not all poor growth is related to pancreatic insufficiency.

Current consensus guidelines recommend that people with CF take PERT before and/or during a meal [202,479].

Does the timing of PERT administration in relation to a meal impact PERT efficacy in people with CF? PICO 10.1.2

[Grade D] Limited evidence suggests PERT is equally effective when taken before or after a meal in people with CF. It also suggests that for some individuals, changing PERT timing in relation to a meal may improve PERT efficacy. A change of PERT timing can be considered for people with symptoms of fat malabsorption or poor growth once other treatment strategies such as adherence have been taken into account. [112]

One study found that PERT was equally effective in promoting normal lipase activity when taken before or after a meal. This study also showed that for some individuals, changing the timing of PERT from before to after a meal, or vice versa, improved or normalised lipase activity [112]. A trial of changing PERT timing in relation to a meal can be considered in those with symptoms of fat malabsorption or poor growth once other treatment strategies such as adherence have been considered.

How should PERT be dosed for people with CF to support optimal fat absorption? PICO 10.1.3

[Grade D] There is inconsistent and insufficient evidence to recommend specific doses of PERT required to support *optimal* fat absorption in people with CF. A wide range of doses have been shown to be effective. [113-131]

Studies looking at optimal PERT dosing in CF differ in enzyme preparation used, dose provided, treatment duration and age of patients. A wide range of doses has been shown to be safe and effective. As a result, practice is likely to vary between clinics on a national and international basis. Despite variations in practice, the following should be considered when recommending PERT dosing in people with CF:

DOSING OF PERT

Practice in Australia and New Zealand is to recommend PERT based on grams of fat consumed. This is due to:

- Improvements in the CFA with this method compared to dosing per meal [515]
- Dosing mimicking the body's physiological response to a meal [516]

Internationally, guidelines give recommendations for both dosing PERT based on units of lipase/kg/meal and units of lipase/g of fat consumed [78,87,132,202]. Dosing per meal and snack has been used due to ease of adherence with this method compared to dosing per gram of fat intake. In clinical trials, both dosing per gram of fat [114,123] and dosing per meal [113,115-117,119-121,124-126,128,129] have been shown to be effective in children and adults.

Guidelines suggest various ranges in which to dose PERT, with a maximum of 2500 IU lipase/kg/meal and 4000 IU lipase/g fat consistently suggested [78,87,132,202]. Two small prospective dose ranging studies of short duration report no improvements in CFA with doses >500 IU lipase/kg/meal [119,120]. Larger retrospective observational studies report conflicting results of no association between PERT dose and growth outcomes [130], and higher BMI percentiles in those with a higher mean PERT dose per kg per day [131].

MAXIMUM DAILY DOSE

A maximum dose of 10 000 IU lipase/kg/day was recommended [516] following observations that doses above 6000 IU lipase/kg/meal [517] and a mean of 50 000 IU lipase/kg/day were associated with fibrosing colonopathy [518]. While this maximum is still generally accepted, the median dose in the control group of the US case-control study investigating fibrosing colonopathy was 13 393 IU lipase/kg/day [518], giving rise to the idea that this maximum may be too conservative. This may be particularly pertinent to neonates and young infants who in the newborn phase may feed up to 12 times per day and therefore may exceed the recommended dose for a short time [519]. It can also be challenging to remain below the maximum suggested dose in individuals with particularly high fat diets or who are on oral or enteral nutrition support.

While there is some suggestion that the maximum of 10 000 IU lipase/kg/day may be exceeded without harm in the short term, this should be done with caution and in consultation and regular review with an experienced gastroenterologist and dietitian. Longer term studies are required to determine whether exceeding the suggested upper limit of 10 000 IU lipase/kg/day for an extended time period is safe. Other factors contributing to poor weight gain and malabsorption related to PERT efficacy such as adherence and timing of PERT in relation to a meal should be considered before increasing PERT dose (see figure 10c). Until further evidence is available, it is recommended that health professionals in Australia and NZ follow the recommendations outlined in table 10c when dosing PERT for people with CF.

Table 10c. Pancreatic enzyme replacement therapy (PERT) - recommendations

PERT Dosing Recommendations	
Infants	Breastfeeds and infant formula • Initiate at 2500-5000 IU lipase per breastfeed or formula feed • Adjust up according to weight gain and bowel symptoms • Maximum of 10 000 IU lipase/kg/day* Solids • Approximately 2000 IU lipase/g fat • Maximum 10 000 IU lipase/kg/day*
Children, Adolescents and Adults	• 500-4000 IU lipase/g dietary fat • Maximum 10 000 IU lipase/kg/day*
General recommendations	• Aim for the lowest effective dose • Use an individualised approach • Distribute PERT throughout the day according to fat content of food and fluid consumed • Monitor weight, growth and bowel symptoms • Individuals should be encouraged to discuss PERT with clinic staff before increasing dose • Branded PERT preparations should be used Distribution • Ensure PERT is correctly distributed over the day's meals based on the fat content of food and drinks consumed Administration • Capsules should be swallowed whole or the granules mixed in with an acidic fruit puree – e.g. apple puree. NB: for infants <6 months of age this is not consistent with recommendations for the introduction of solids, however is appropriate in CF • Granules should not be chewed • PERT should be given with all meals, snacks and food containing fat • PERT may be given before, during or after a meal Physical Storage • Store capsules in an airtight container in a cool, dry place. In warmer climates it may be necessary to store the product in the refrigerator to maintain storage below 25°C – see specific product information for more information on storage • Ensure capsules have not exceeded the expiry date

Adapted from international recommendations: Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis [87] Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review [132], ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis[375] and the Australasian Clinical Practice Guidelines for Nutrition in CF [1] .

* In some situations the upper limit may need to be exceeded in the short term, such as infants feeding frequently – this should be done with caution and with regular review by a gastroenterologist and dietitian.

ENTERAL FEEDING

There is little evidence to support how PERT is best administered and optimised in people with CF receiving enteral nutrition. In the absence of sufficient evidence, a number of techniques have been described [479,520,521] including:

- Oral administration
- PERT suspended in juice
- PERT dissolved in bicarbonate and administered via an enteral feeding tube
- Administration of crushed microspheres via an enteral feeding tube

A variety of dosing options for administration of PERT during continuous feeds have also been described [483] including:

- Administration of the entire dose of PERT before a feed
- Administration of multiple doses every 3 hours during a feed

It has been suggested that enzyme activity in the gut is negligible after two to three hours and it may be appropriate to administer a lipase dose which matches the amount of fat to be delivered over three hours of continuous feeding [522]. Until further evidence is available, the following options are suggested for dosing PERT with enteral feeds:

ORAL ADMINISTRATION OF PERT

Where possible, PERT should be taken orally with enteral feeds. See figure 10b for possible options for PERT dosing with enteral feeds.

ENTERAL ADMINISTRATION OF PERT

There are situations where oral administration of PERT with enteral feeds may not be possible such as in neonates without the ability to swallow. There is insufficient evidence to provide specific recommendations for administration of PERT via an enteral feeding tube. It is important that an interdisciplinary and individualised approach including a dietitian and, where relevant, advice from experienced professionals such a gastroenterologist, neonatologist, respiratory physician and pharmacist is used when determining the method of PERT administration via a feeding tube. In centres where experienced professionals are not available, advice should be sought from a major CF centre for areas of uncertainty. Things to consider when determining the method of administration when oral administration is not possible include:

- Size of feeding tube – smaller feeding tubes may become blocked more easily
- Dissolution rate of enzymes when administered in bicarbonate – this may vary across PERT products and doses [523]
- Risk of metabolic alkalosis with bicarbonate administration
- Efficacy of PERT when crushed – enzymes may not be as efficacious when crushed and added to feed

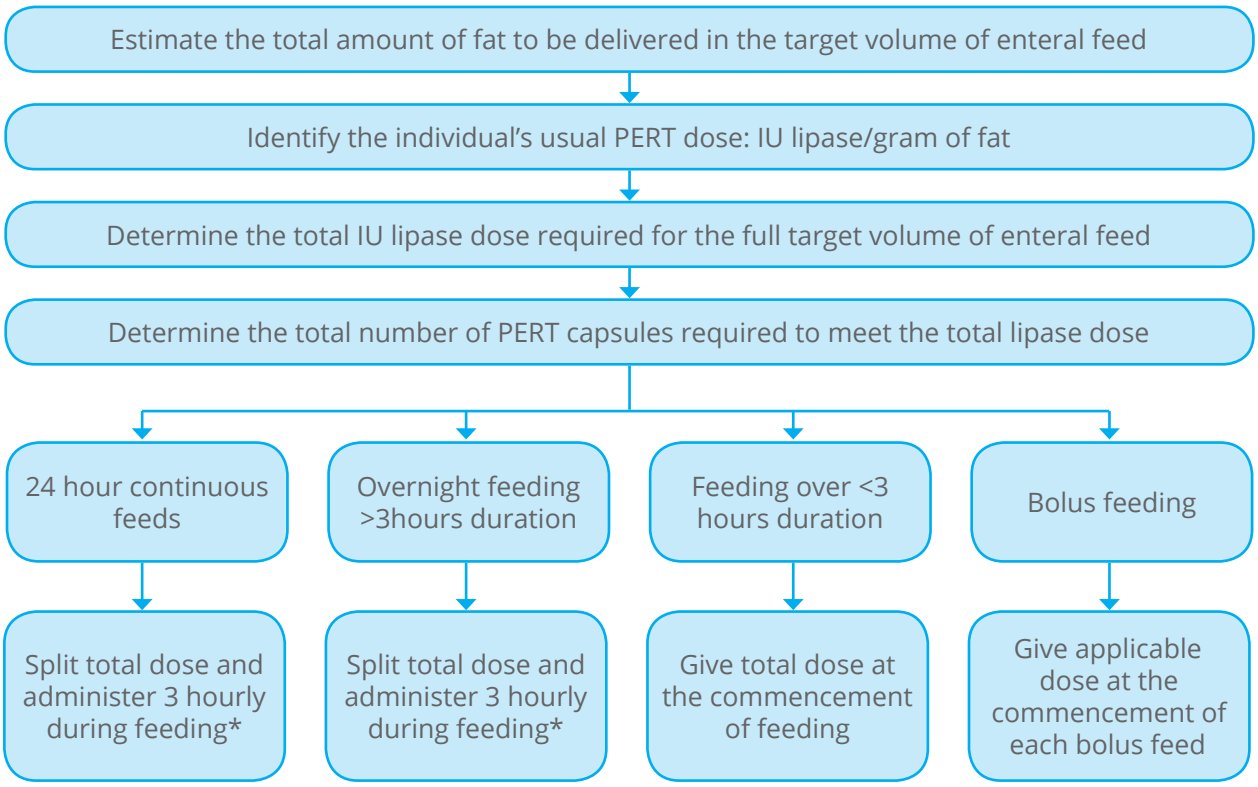

Figure 10b. Suggested dosing options for oral administration of pancreatic enzyme replacement therapy (PERT) with enteral feeds.

**In those who do not voluntarily wake or do not wish to wake overnight it may be more practical to give 50% of PERT dose at the commencement of feeding and 50% at the end.*

Additional considerations when determining administration of PERT with enteral feeds:

- **Sleeping patterns** – in patients who take PERT orally and do not voluntarily wake or do not wish to wake overnight, it may be more practical to determine total PERT dose required and give 50% of PERT dose at the commencement of feeding and 50% at the end of feeding.
- **Type of feed** – while there is little evidence as to the efficacy of elemental or semi-elemental feeds over polymeric feeds in CF, it is thought that semi-elemental and elemental feeds may be more easily absorbed without PERT due to the high proportion of total fat as MCT, however, for many patients, sufficient energy and nutrient intakes cannot be achieved with the use of elemental or semi- elemental feeds, due to their lower energy density.
    - An individualised approach should be employed when determining PERT use with elemental or semi-elemental feeds.
    - Clinical symptoms and weight gain should be monitored when determining need for PERT and dose required.
- **Family and patient preference** – it is important to work in partnership with patients and their families to develop an enteral feeding and PERT regimen that fits in with the patient's nutritional needs as well as their lifestyle.

ADJUNCT THERAPY

In people with CF and pancreatic insufficiency, the pancreas has an impaired ability to secrete bicarbonate, which can result in duodenal hyperacidity and impaired acid neutralisation [524,525]. This can lead to significantly longer periods where duodenal pH is below 4.0 in the post prandial period [526]. Most PERT preparations show 90% or greater dissolution rate within 30 minutes at a pH greater than 5.8 [527]. The lower duodenal pH in CF may therefore impair the release of enteric coated PERT, reducing their efficacy. In theory, acid suppression medication as an adjunct therapy to PERT may increase the pH of the duodenum, aiding acid neutralization and subsequently assisting PERT function therefore improving fat digestion and absorption. Early studies exploring this theory showed promising results when high doses of PERT were consumed [528].

Is there evidence to support the use of acid suppression medications to improve PERT efficacy for people with CF? PICO 10.1.4

[Grade C] There is inconsistent and limited evidence to support for or against the use of acid suppression medication to improve PERT efficacy by increasing fat absorption for people with CF. Further research is required. [133-135]

A Cochrane review investigating drug therapies for reducing gastric acidity concluded that trials have shown limited evidence that agents that reduce gastric acidity improve fat absorption [135]. Additional studies looking at acid suppression medications and PERT efficacy in CF have shown:

- Faecal fat loss decreased significantly in CF children on high dose PERT (>10 000 IU lipase/kg/d) with residual steatorrhoea after 10-20mg daily omeprazole for one month [133].
- Ranitidine as adjuvant therapy to pancrelipase in children with CF, and ranitidine and omeprazole as adjuvant therapy to pancrelipase in adults with CF, had no benefit on fat absorption [134].

ACUTE PANCREATITIS AND PERT

There is limited information specific to CF on PERT dosing in acute pancreatitis. For information on PERT dosing in acute pancreatitis in general, refer to the *Australasian guidelines for the management of pancreatic exocrine insufficiency* [498].

Monitoring & Evaluation

Efficacy and safety of PERT

All studies included in this review concluded that PERT is safe and efficacious at doses in line with current guidelines [78,132]:

- <2500 IU lipase/kg/meal OR <4000 IU lipase/g of fat
- <10 000 IU lipase/kg/day

Safety was assessed by adverse event occurrence and efficacy assessed by improvements in weight or CFA. Most studies were generally short in duration with treatment periods ranging from 3-28 days [115,118-124,127-129,529], while other studies were up to 3 months [116], 12 months [125,126] or 2 years [113].

Both Panzytrat® and Creon® have been deemed safe by the TGA (www.tga.gov.au). It is recommended that branded PERT preparations are used to ensure efficacy [132] (see table 10a).

GENETIC MODULATOR TREATMENTS

A recent study in children 2-5 years of age showed significant improvements in faecal elastase concentration after treatment with Ivacaftor, with some subjects converting from abnormal to normal faecal elastase concentrations after 24 weeks of treatment [530]. A small case report has also shown that Ivacaftor treatment has normalised faecal fat excretion and in some individuals, PERT therapy can be withdrawn [531]. It is not yet known if the same observations will be made with other genetic modulator treatments. PERT requirements for patients on Ivacaftor or other genetic potentiator and genetic modulator treatments should be assessed on an individual basis by an experienced CF team. Further information regarding genetic modulator therapy is available in **Chapter 14**.

PHTHALATES

What are the risks and long-term health implications associated with phthalate exposure via PERT to people with CF? PICO 10.1.5

[Ungraded] There is insufficient evidence to make a CF-specific recommendation.

Phthalates are a family of chemicals commonly found in everyday objects, including construction materials, furnishings, plastics, pharmaceuticals, solvents and cosmetics [532] and are generally classified according to their molecular weight. Most research into the safety of long-term exposure to phthalates has been conducted in animal studies. Small human epidemiological studies, however, have found a weak association between phthalate exposure and poor fertility, miscarriage, pre-term births and low birth weight infants [533]. Prenatal phthalate exposure has also been found to impact male reproductive development [534,535].

Some commonly used CF medications, including Creon®, contain phthalates in their enteric coating to help withstand the acidic environment of the stomach [536]. A 2009 Canadian study found measurable levels of phthalate compounds in the urine of CF children on PERT containing the low molecular weight phthalates diethyl phthalate and dibutyl phthalate [537]. Since then, all Creon® products in Australia and NZ no longer list dibutyl phthalate as an inactive ingredient. Instead, they now contain hypromellose phthalate, a high molecular weight polymer that does not convert to potentially harmful monoesters [538]. The risk of phthalate polymer toxicity is considered to be low or not known [539]. In Australia the TGA lists phthalate polymers as an ingredient for use in prescription medications without any restriction (www.tga.gov.au) and both Panzytrat® and Creon® are approved by the TGA. Exposure to phthalates via PERT should therefore not be of concern to the CF population.

Panzytrat 25 000® does not contain phthalates or the HMP polymer.

MONITORING OF PERT

PERT use should be monitored and reviewed regularly by the dietitian and interdisciplinary team in people with CF; at every clinic visit for infants, every 3 months for older children and adolescents, and every 6 months for adults [78]. Reviews should include ongoing education and support for people with CF that promotes PERT adherence. Self-management should gradually be introduced throughout the paediatric years, especially leading into and throughout adolescence.

If the response to a prescribed PERT dose is inadequate, adherence should first be addressed. This includes a review of PERT dose to ensure appropriate distribution of PERT to fat content. If adherence is considered adequate and PERT is appropriately distributed according to fat content, the following should also be considered (as outlined in figure 10c):

- Quantification of steatorrhoea
- Timing of PERT – a trial of changing the timing of PERT around the meal may be beneficial, particularly in those with suspected altered gastric emptying
- Methods used for PERT storage
- Referral to a gastroenterologist to consider and investigate potential gastrointestinal complications including role of gastric emptying rate (± formal gastric emptying assessment)

Once these factors have been considered and addressed, PERT doses can be increased over time to a maximum of 10 000 IU lipase/kg/day. PERT doses should not be indiscriminately escalated without establishing a clear rationale and a plan for evaluating the impact of the alteration in doses. This is particularly important given reports suggest a higher PERT dose is not associated with a reduction in gastrointestinal symptoms such as gas, constipation and stomach ache or reduction in number of stools [130].

Despite a lack of conclusive evidence, a trial of a proton pump inhibitor may be initiated once all other strategies to improve adequacy have been exhausted. It is important that use of a protein pump inhibitor is monitored, given mounting evidence that proton pump inhibitors are associated with significant side effects including an increased risk of fracture, hypomagnesemia and lower serum iron levels in the non-CF population [540], and may be associated with a trend toward earlier and more frequent pulmonary exacerbations in the CF population [139].

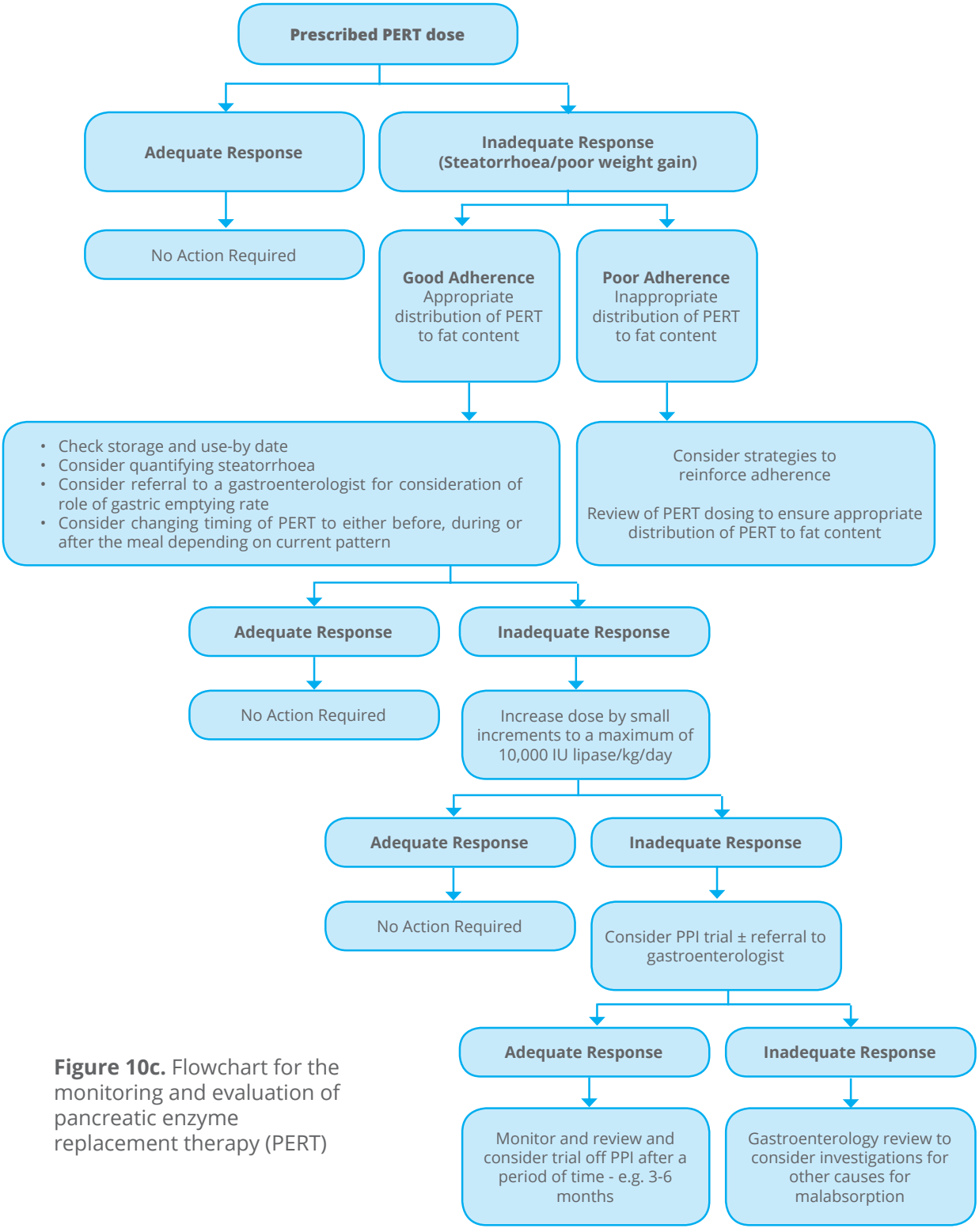

Figure 10c. Flowchart for the monitoring and evaluation of pancreatic enzyme replacement therapy (PERT)

Practice Points PICO 10.1.1 and 10.2.2

Prior to changing the timing of PERT in patients with symptoms of fat malabsorption and poor growth evaluate:

- Is the patient compliant with PERT?
- Is PERT distributed appropriately according to fat content?

Explore the role of gastric emptying rate and referral to a gastroenterologist for consideration (± formal gastric emptying assessment). People with fast gastric emptying may benefit from taking PERT before a meal.

Practice Points PICO 10.1.3

PERT Dosing Recommendations

Dosing recommendations adapted from international recommendations:

- *2006 Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis*[1]
- *2008 Evidence-Based Practice Recommendations for Nutrition-Related Management of Children and Adults with Cystic Fibrosis and Pancreatic Insufficiency*[132]
- *2009 Cystic Fibrosis Foundation evidence-based guidelines for the management of infants with cystic fibrosis*[87].
- *2016 ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis*[78]

Infants

- Breastfeeds and Infant Formula
  - Initiate at 2500-5000 IU lipase per breastfeed or formula feed and adjust up according to weight gain and bowel symptoms to a maximum of 10 000 IU lipase/kg/day*
- Solids
  - Approximately 2000 IU lipase/g fat
  - Maximum 10 000 IU lipase/kg/day*

Children and Adults

- 500-4000 IU lipase/g fat.
- Maximum 10 000 IU lipase/kg/day*

General PERT recommendations

- Aim for the lowest effective dose
- Use an individualised approach
- Distribute the enzymes throughout the day according to the fat content of food and drinks consumed
- Monitor weight, growth and bowel symptoms
- Individuals should be encouraged to discuss PERT with clinic staff before increasing dose
- Branded PERT preparations should be used

Distribution

Ensure PERT is correctly distributed over the day's meals based on the fat content of food and drinks consumed

Administration

- Capsules should be swallowed whole or the granules mixed in with an acidic fruit puree – e.g. apple puree. Granules should not be chewed
- PERT should be given with all meals, snacks and food containing fat
- PERT may be given before, during or after a meal**

Physical Storage

Store capsules in an airtight container in a cool, dry place – see specific product information for more information on storage. Ensure capsules have not exceeded the expiry date

* In some situations the upper limit may need to be exceeded in the short term, such as infants feeding frequently – this should be done with caution and with regular review by a gastroenterologist and dietitian

**new recommendation

Practice Points PICO 10.1.4

Take into account the following prior to commencing acid suppression medication in people with CF with symptoms of steatorrhoea and on high dose PERT:

- Is the patient adherent with PERT?
- Is PERT distributed appropriately according to fat content?
- Role of gastric emptying rate and referral to a gastroenterologist for consideration (± formal gastric emptying assessment)
- Increasing the dose by stepwise increments to a maximum of 10 000 IU lipase/kg/day
- If a trial of acid suppression medication is commenced review its effect regularly, e.g. 3-6 monthly

Practice Points PICO 10.1.5

Provide people with CF and their families with the latest information regarding phthalates and PERT on request.

Phthalate polymers, including hypromellose phthalate (HMP), are non-active ingredients in the enteric coating of many medications, including all Creon® products available in Australia and NZ.

- Unlike other phthalates that degrade to potentially harmful monoesters, phthalate polymers are considered to be of low or no known toxicity risk.
- In Australia the Therapeutic Goods Administration (TGA) lists phthalate polymers as an ingredient for use in prescription medications without any restriction (www.tga.gov.au).

All PERT products in Australia are approved by the TGA for use, therefore concern about phthalates is not an indication on its own for changing the choice of PERT preparation. Exploring such a change for an individual should be based on factors such as adequacy of control of malabsorption, and/or the occurrence of side effects.

Panzytrat 25 000® does not contain phthalates or the HMP polymer.

Translating into Practice

Determining PI

Local guidelines should be used when determining which test to use to assess pancreatic status.

Assessing PERT adequacy

Local guidelines should be used when determining how to assess PERT adequacy. The FFB test is considered the gold standard, however it is not commonly used in practice due to its cumbersome nature. It may be more practical to consider symptoms such as poor weight gain and/or weight loss in conjunction with abdominal pain, abdominal distention, gas, frequent stooling and steatorrhoea when assessing PERT adequacy.

General Tips

- A 3 day food and enzyme diary may assist in assessing PERT dose adequacy
- Providing a capsule container may assist transport of PERT and improve adherence
- PERT is reported to be effective for 30 minutes after consumption
  - For slow eaters/feeders or meals/feeds extended over a longer duration the total dose required may be split and half given at the commencement of a meal and half during or towards the end.
- PERT may be dosed per meal and snack for those who are unable to or choose not to fat count
  - Maximum of 2500 IU lipase/kg/meal has been recommended with half of meal dose given for snacks
- Requirements for PERT can change over time
- An individualized PERT plan should be discussed with the CF dietitian taking into account different environments e.g. school, university, socialising, eating out, workplace etc.
- Monitor for unnecessary increases in PERT dose
- Monitor for out of date enzymes and incorrect storage (such as in a hot car) when symptoms of malabsorption and/or poor growth are reported

...table continued overleaf

Neonates

Discuss initiation of PERT with the neonatal team if titrating from total parenteral nutrition (TPN) onto oral and/or enteral feeds. PERT is often commenced when enteral or oral feeds are at 50% of the target volume.

Infants

Available preparations:

- Australia - Creon micro® is the only PERT preparation acceptable for use
- NZ - Creon micro® is not available. Creon 10 000® is used as an alternative

Administration:

1. Place PERT granules in a small amount of acidic puree (e.g. apple puree) on the tip of a soft baby spoon
2. Place spoon under the top gum and scrape upwards, leaving the PERT and apple puree in the mouth
3. If the infant spits the mixture out, scrape it up with the spoon and repeat the above process
4. At completion of a feed, check the infant's gums for any remaining granules and remove with a clean finger as the PERT may cause mouth ulcers

Timing:

- Administer PERT immediately prior to the feed
- If feeds take >30minutes, a split dose (e.g. half at the beginning and half in the middle or end of the feed) may be required
- For infants feeding frequently, the lowest and most effective dose should be used, given frequent feeds are likely to be small in volume
- Introduction of solids:
    - PERT may not be needed with solids until greater than a tablespoon of fat containing food is consumed

Children

- Children should be switched from PERT granule preparations to PERT capsule preparations when they can swallow medications
- Tips to improve adherence:
    - PERT can be taped to foods in school lunchbox
    - The amount of PERT required with each meal and snack can be written down and provided to care-givers and teachers and/or placed in the child's lunchbox

Adolescents

- Adherence to therapies, including PERT can be challenging
    - Changing to a higher dose preparation e.g. Creon 25 000® may reduce pill burden and increase adherence, but alert to unnecessary increased in PERT dose
- Dietary intake patterns and behaviours may change (e.g. increased consumption of takeaway foods)
    - More regular review of PERT dosing may be required
    - Re-education of PERT dosing strategies including label reading may be beneficial
- Increased autonomy with PERT administration is encouraged
    - Be aware that PERT doses may be increased unnecessarily
    - An upper meal and snack dose limit guide may be beneficial for this population group

Adults

- Accuracy in identifying the fat content of meals and snacks may vary widely within and between days
    - More regular review of PERT dosing may be required
    - Re-education of PERT dosing strategies including label reading may be beneficial
- Review for unnecessary increases in PERT doses, especially in adults with persistent gastrointestinal complaints
    - Adults may increase doses of PERT to manage gastrointestinal symptoms.
    - Additional causes for GI symptoms should be reviewed to prevent unnecessary increases in PERT