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Pancreatic exocrine insufficiency (PEI) and pancreatic enzyme replacement therapy (PERT) in pancreatic cancer

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Content & learning outcomes

- Pancreas anatomy & physiology
- Pancreatic Exocrine Insufficiency (PEI)
    - Causes
    - Consequences
    - Symptoms
    - Diagnosis
- Pancreatic Enzyme Replacement Therapy (PERT)
    - Who benefits from PERT
    - What it does
    - How to take it effectively
    - Titrating dose
    - PERT & enteral feeding
- Summary

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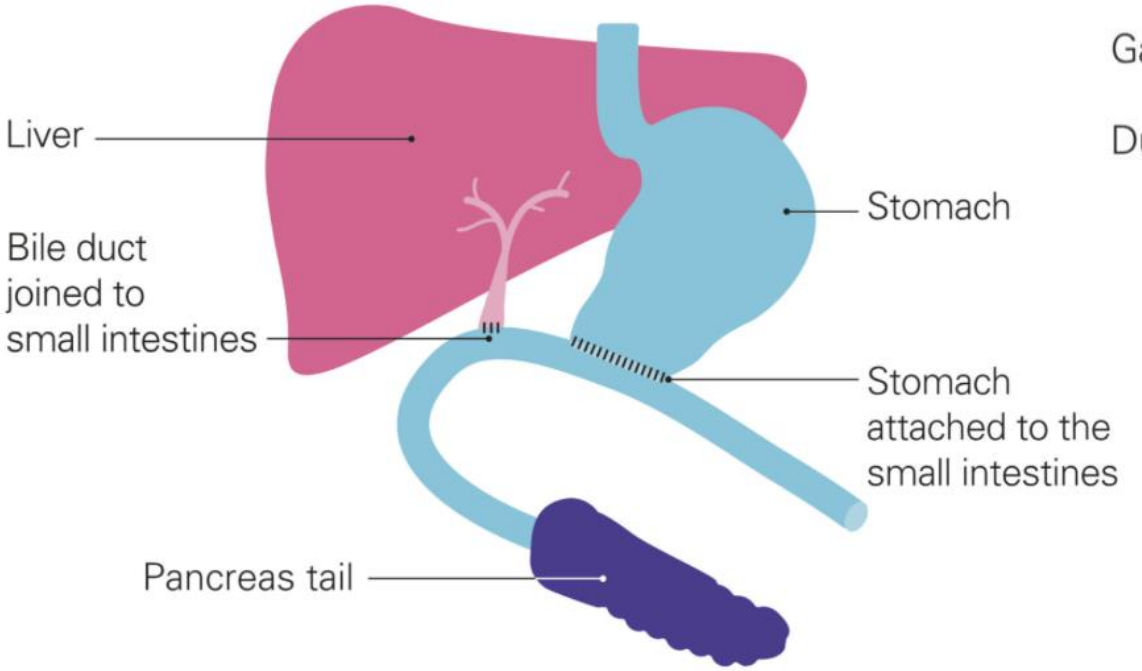

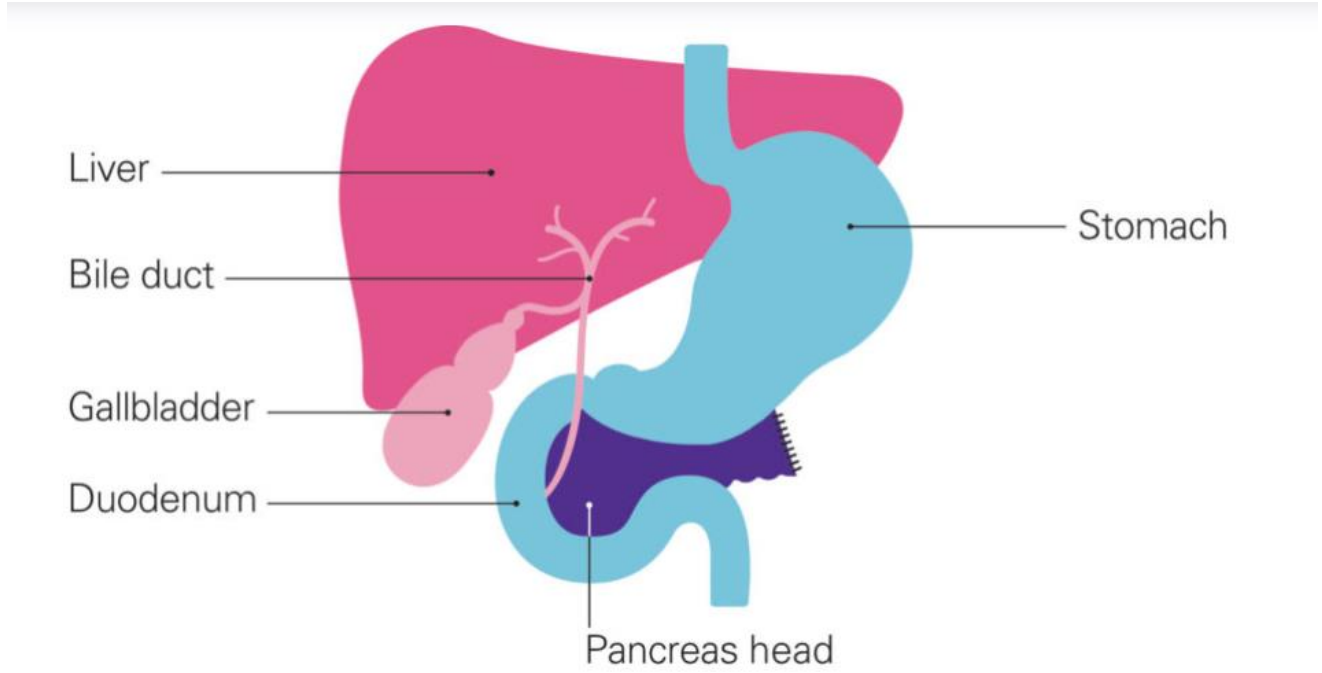

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Digestive enzymes

	Carbohydrate	Fat	Protein
Saliva	Amylase	Salivary lipase	
Gastric	Gastric amylase	Gastric lipase	Pepsin, rennin, gelatinise
Pancreas	Amylase	Lipase, Steapsin	Trypsin, elastase, chymotrypsin, Carboxypeptidase
Duodenum/Ileum	Sucrase, maltase, lactoase, isomaltase	Intestinal lipase	BB peptidases

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Pancreatic Exocrine Insufficiency (PEI)

Definition

"a reduction in pancreatic enzyme activity in the intestine at a level that prevents normal digestion"

Consensus for the management of PEI: UK practical guidelines (Phillips et al 2021)

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Causes of PEI

Primary

- Pancreatic cancer
- Surgery:
    - PPPD/Whipples
    - Distal
    - Central
    - Total
    - Enucleation
    - Benign procedures eg Frey's
- CP
- SANP
- CF

Secondary

- Post op asynchrony
- Gastric/duodenal resections
- Medications eg Octreotide

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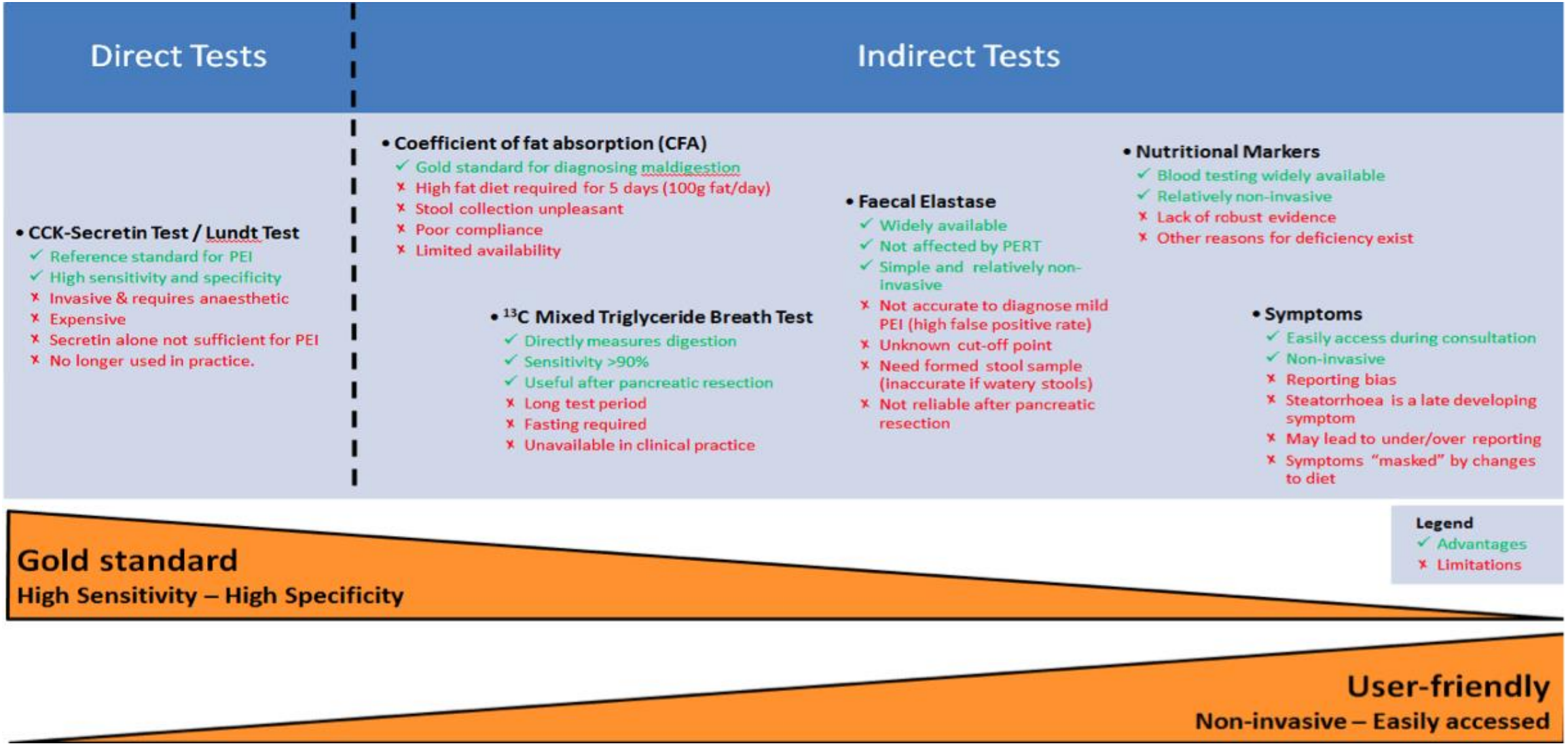
Diagnosis



Carnie et al 2020

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Diagnosis

Box 1 Diagnosis of PEI

PEI is highly likely with high benefit from PERT: no further test required as significant benefit from treatments and the negative predictive value of FEL-1 is not strong enough to prevent starting treatment

- Head of pancreas cancer
- Pre-surgery and post-surgery for head of pancreas cancer with or without pylorus preserving operation
- Total pancreatectomy
- Steatorrhoea or malabsorption symptoms in patients with CP with dilated pancreatic duct or severe pancreatic calcification
- Severe necrotising pancreatitis

Patients that require initial investigation with FEL-1

- GI symptoms of maldigestion in secondary care with or without known associated conditions
- Maldigestion symptoms: steatorrhoea, weight loss, diarrhoea, abdominal pain or bloating
- Associated conditions: patients with coeliac disease, IBS-D, HIV, type 1 diabetes and acute severe pancreatitis after initial phase

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Pancreatic Exocrine Insufficiency (PEI)

Symptoms:

- Steatorrhea (pale, oily, greasy, yellow/orange stools)
- Diarrhoea
- Bloating/wind
- Colicky abdo pain (esp after food)
- Borborygmi

Secondary symptoms:

- Weight loss (despite good intake)
- Reduced functional status
- Fat soluble vitamin deficiencies
- Hypoglycaemia/unstable glycaemic control
- Poor wound healing
- Other markers of malnutrition eg. Mg, RBP (in correlation)

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Pancreatic Enzyme Replacement Therapy (PERT)

Locally:

- All patients with a diagnosis of pancreatic cancer (head, tail, body, ampullary)
- Distal cholangiocarcinoma
- Duodenal (dependant on symptoms)

Advice to commence enzymes on MDT proforma back to local hospital

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Pancreatic Enzyme Replacement Therapy (PERT)

Pancreatic enzyme replacement therapy in patients with pancreatic cancer: A national prospective study

The RICOCHET Study Group on behalf of the West Midlands Research Collaborative[12]

1350 pts:

- 74% resectable v 45% unresectable prescribed PERT
- Significantly associated with Dietitian referral/specialist unit
- Wide variation & under-treatment of PERT

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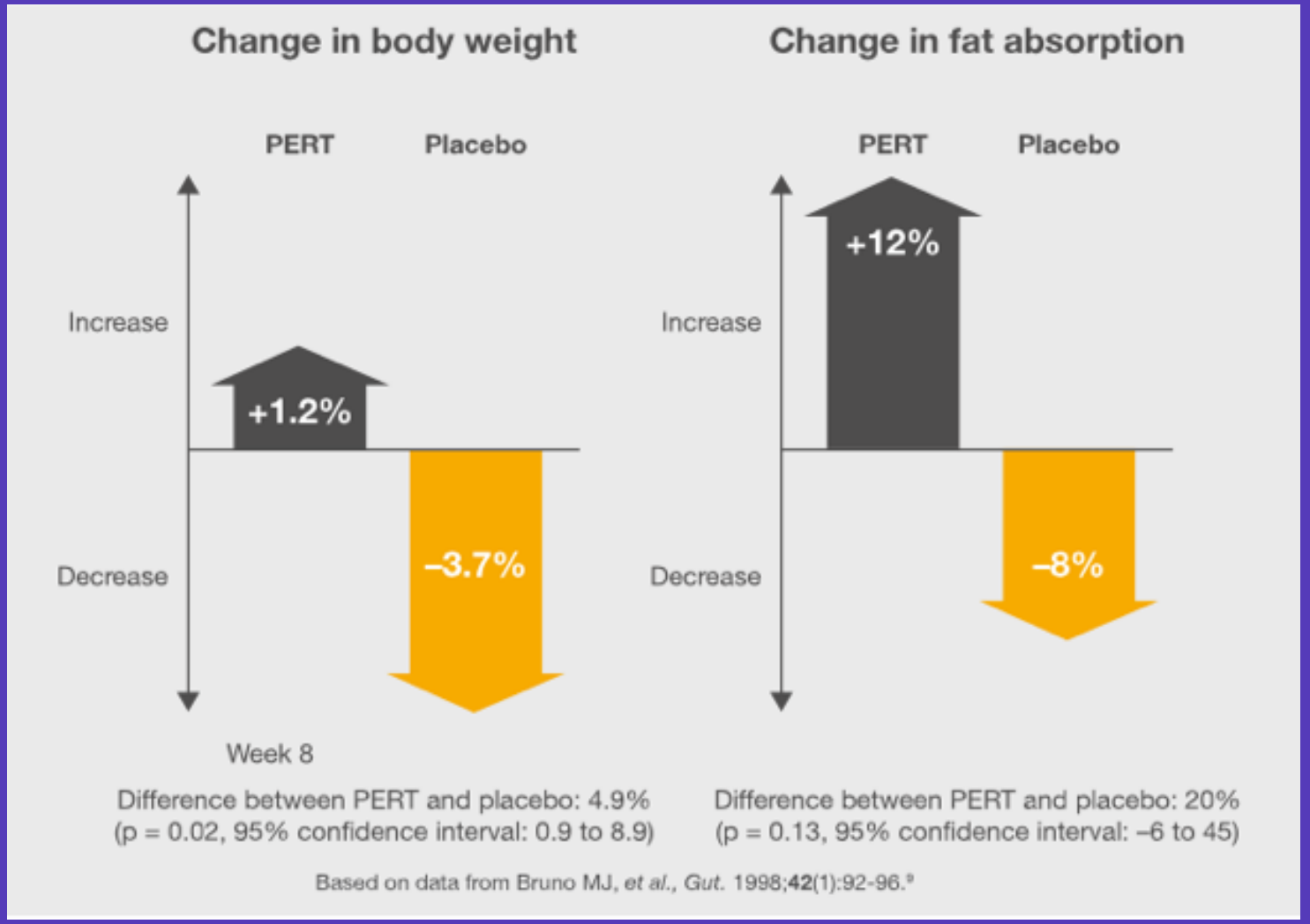
Pancreatic Enzyme Replacement Therapy (PERT)



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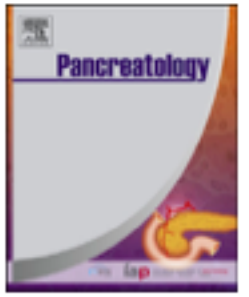
Pancreatic Enzyme Replacement Therapy (PERT)

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan



Enzyme replacement improves survival among patients with pancreatic cancer: Results of a population based study

K.J. Roberts [a, *], C.A. Bannister [b], H. Schrem [c]

[a] Honorary Reader and Consultant Surgeon, Institute of Immunology and Immunotherapy, University of Birmingham, UK
[b] Digital Health Laboratories, UK
[c] Consultant Surgeon, Dept Visceral, General and Transplant Surgery, Hannover Medical School, Germany

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Pancreatic Enzyme Replacement Therapy (PERT)

Pancreatic cancer in adults: diagnosis and management

NICE guideline

Published: 7 February 2018

nice.org.uk/guidance/ng85

1.6 Nutritional management

1.6.1 Offer enteric-coated pancreatin for people with unresectable pancreatic cancer.

1.6.2 Consider enteric-coated pancreatin before and after pancreatic cancer resection.

BMJ Open Gastroenterology

Consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines

Mary E Phillips ,[1] Andrew D Hopper,[2] John S Le
Laura McGeeney,[5] Sinead N Duggan,[6] Rajesh Kun

European countries.[11] Patient support groups report management of PEI as the most common concern raised on their patient helpline (Pancreatic Cancer UK, 2015),

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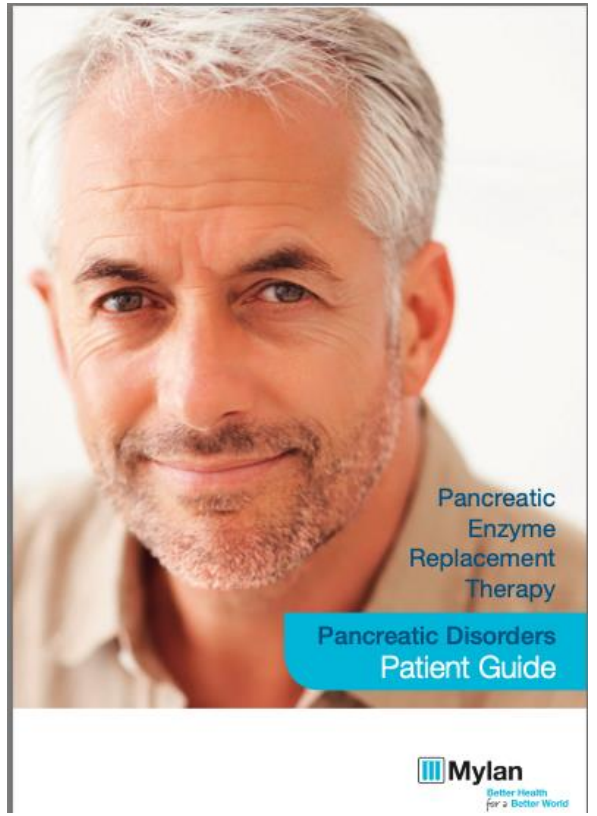
Pancreatic Enzyme Replacement Therapy (PERT)

Right place, right time, right pH…aim to mimic action of pancreas:

- Nutritional coaching
- Patient education on what enzymes are/how they work etc
- Treat like insulin
- Likely to need more post op, hospital diet not normal!
- Different times, different meals, different days
- Eating out
- Monitoring symtoms



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PERT preparations

	Amylase	Lipase	Protease
Pancrex V 125mg capsules	3300u	2950u	160u
Pancrex V capsules	9000u	8000u	430u
Creon 10 000 capsules	8000u	10 000u	600u
Creon 25 000 capsules	18 000u	25 000u	1000u
Nutrizym 22 capsules	19 800u	22 000u	1100u
Pancrease HL capsules	22 500u	25 000u	1250u
Creon Micro granules	3600u	5000u	200u
Pancrex V powder (1g)	30 000u	25 000u	1400u

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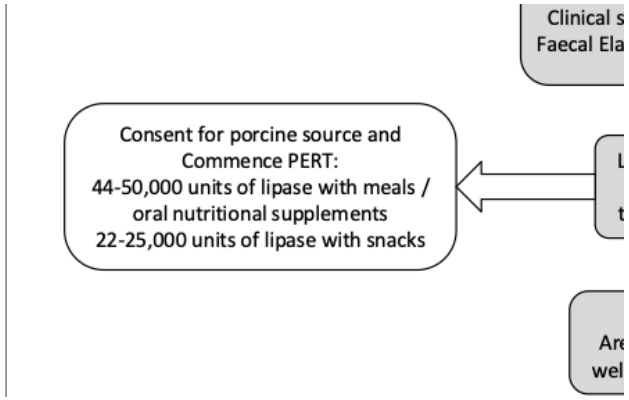
Pancreatic Enzyme Replacement Therapy (PERT)



Phillips et al 2021

- Gain consent for porcine nature of enzymes
    - Failed trail of non-porcine based
    - Vegetarian/vegan

Side-effects

Common or very common

Abdominal distension; constipation; nausea; vomiting

Uncommon

Skin reactions

Frequency not known

Fibrosing colonopathy

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Pancreatic Enzyme Replacement Therapy (PERT)

Statement 4.2: PERT should be started at a dose of at least 50 000 units lipase with meals and 25 000 units lipase with snacks (grade 1A), and patients should be encouraged to adjust their dose if this is ineffective (grade 2C) (92% agreement)

The choice of PERT preparation needs to consider the lipase units the patient requires and the number and size of capsules the patient is able to swallow. Studies support the use of at least 50 000 units lipase as a suitable starting dose with meals and 25 000 units lipase with snacks.[91 98] All guidelines endorse dose escalation if the initial dose is not effective.[77 99 100]

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Pancreatic Enzyme Replacement Therapy (PERT)

Poll

How do you advise patients to take oral enzymes?

1. Before meals/snacks
2. After meals/snacks
3. Alongside meals/snacks
4. Before & after meals/snacks

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Effect of the administration schedule on the therapeutic efficacy of oral pancreatic enzyme supplements in patients with exocrine pancreatic insufficiency: a randomized, three-way crossover study

J. E. DOMÍNGUEZ-MUÑOZ*, J. IGLESIAS-GARCÍA*, M. IGLESIAS-REY*, A. FIGUEIRAS† & M. VILARIÑO-INSUA*

*Departments of *Gastroenterology and †Clinical Epidemiology, University Hospital of Santiago de Compostela, Santiago de Compostela, Spain*

- Randomised, 3 way 1 week cross-over design
- CP population
- 24 pts
- 3 schedules: just before, just after meals, or distributed along with meals
- C-triglyceride breath test before/during treatment

But…

- CP anatomy/physiology
- Small sample
- Strict exclusion criteria
- PERT still effective if taken in one go

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ORIGINAL ARTICLES

Frequency of Appropriate Use of Pancreatic Enzyme Replacement Therapy and Symptomatic Response in Pancreatic Cancer Patients

Barkin, Jodie A. MD*; Westermann, Amy MPH†; Hoos, William MS, MBA†; Moravek, Cassadie BS†; Matrisian, Lynn PhD, MBA†; Wang, Hongwei MS‡; Shemanski, Lynn PhD‡; Barkin, Jamie S. MD*; Rahib, Lola PhD†

- 262 PCAN pt registry
- Questionnaire on PERT
- PERT with meals = less symptoms, compared to before/aft
  = weight gain

But, consider pill burden

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Ongoing symptoms:

- Check how they are administered
- Check how much the patient is taking
- Check prescribed dose
- Diet assessment (check snacks, milk, milky drinks, ONS, higher fat meals, “healthy” high fat foods/snacks, hot drinks cooled, multiple courses)
- Check storage
- Check swallowing
- Opening capsules?
- Check not out of date

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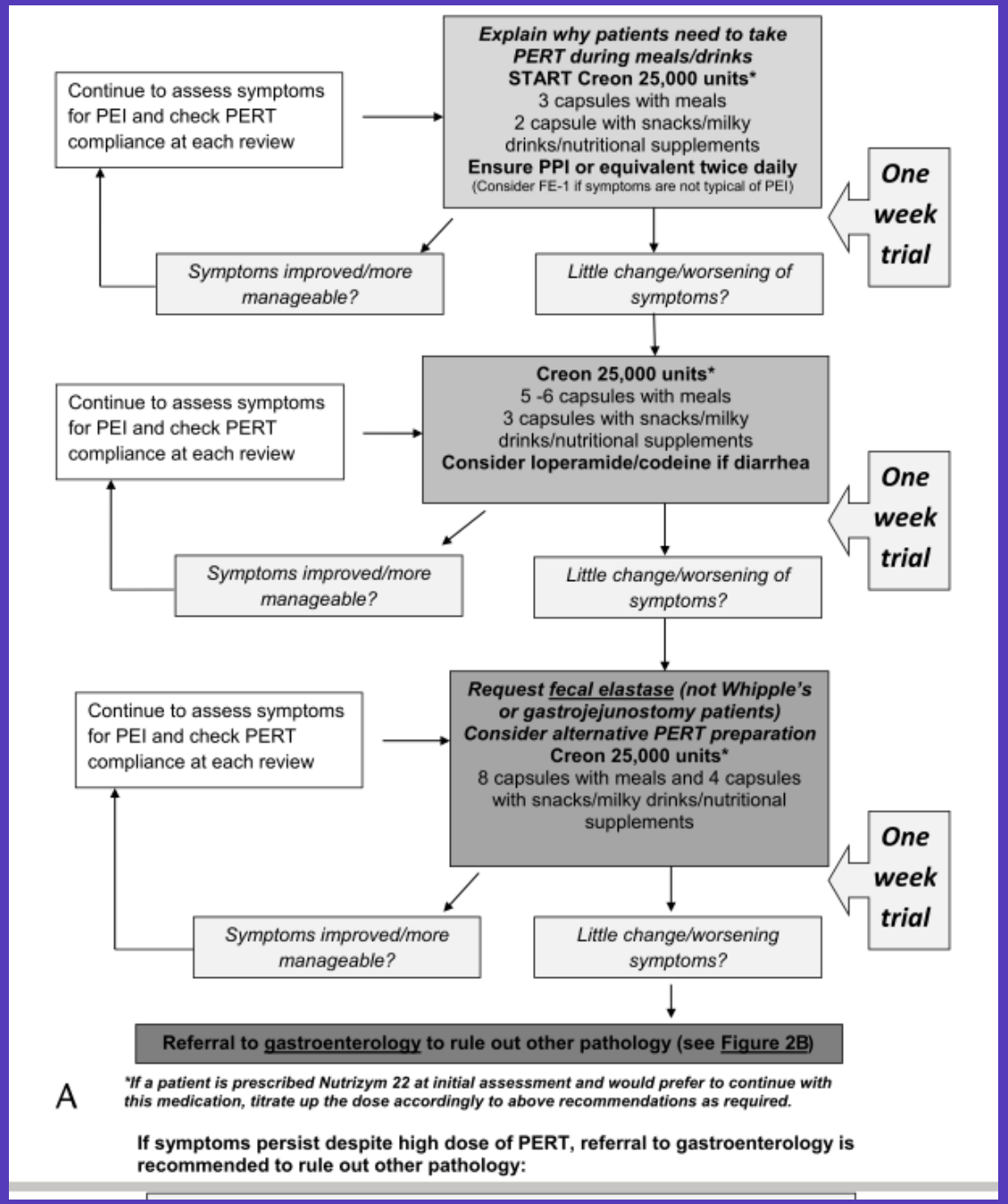
- PPI (dose/frequency)
- Dose escalation
- Loperamide/Codeine
- Alternative preparation
- Referral to gastroenterology:
  - ?BAM
  - ?SIBO
- Other conditions:
  - Disease progression
  - IBS



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Problem: combining PERT with enteral feeding

How are enzymes used along side enteral feeds?

- Variables:
  - Enzyme type/brand/presentation
  - Patient setting eg ICU, ward, pts home
  - Tube type eg naso- or percutaneous
  - Tube end point location/pH environment eg gastric v jejunal
  - Tube lumen gauge (6-24Fr)
  - Feeding regimen inc duration, rate, continuous, bolus
  - Patient's degree of pancreatic function
  - Patients who also eating/drinking

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Type of feed

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

ESPEN Guideline

ESPEN guideline on clinical nutrition in acute and chronic pancreatitis

Marianna Arvanitakis [a, *], Johann Ockenga [b], Miha
Željko Krznarić [e], Dileep N. Lobo [f, g], Christian Lös
Mary Phillips [k], Henrik Højgaard Rasmussen [l], Jean

In patients with AP a standard polymeric diet shall be used.

Grade of Recommendation A – Strong consensus (97% agreement).

- ESPEN 2020 recommends polymeric feeds
- Based on meta-analysis (Poropat et al 2015)
- No evidence to support specific formula
- Severe AP may need semi-elemental

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Enteral feeding

- Phillips et al (2021) recommends peptide feeds
  - Consider total fat content, % MCT,
- Feeds still contain significant LCT, therefore need enzymes

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Enzyme capsules

- Enteric coated microspheres in gelatine capsule
- Enzymes work in specific pH, alkaline environment is optimal:
    - pH <4 denatured
    - >5.5 not activated (enteric coating not broken down)
- Pancreatic bicarbonate production impaired in PEI
- Gastric acid hypersecretion can exacerbate function

Problem:
combining PERT with enteral feeding

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Literature review

Techniques and Procedures

Pancreatic Enzyme Supplementation for Patients Receiving Enteral Feeds

Suzie Ferrie, RD, MNutrDiet[1]; Christie Graham, RD, MNutrDiet[2]; and Matthew Hoyle, RD, BNutrDiet(Hons)[3]

Financial disclosure: none declared.

Nutrition in Clinical Practice
Volume 26 Number 3
June 2011 349-351

10.1177/0884533611405537
http://ncp.sagepub.com
hosted at
http://online.sagepub.com

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- Jejunal tubes: enzymes require activation - crush microspheres, mix with alkaline agent (or leave to dissolve in solution for 20mins)

- Gastric tubes: thickened “nectar consistency” acidic fluid

- Starting dose: 10 000u/g fat. Calculate total enzyme requirement, distribute 2-3hourly, or before overnight feed

eg. 1500mls Survimed OPD HN x12 hours = 42g fat: 6 doses of 7000u 2hourly, 4 doses of 10 500u 3hourly

- Overnight feeds: 3hourly dose/50% total at start

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Limitations

- >10-12Fr tubes use smallest microspheres eg 5000u or micro granules
- Crushing not advised in UK
- Significant stand time + impact on nursing/patient's time
- No accounting for MCT proportion of feeds
- Australian paper (non-enteric coated products no longer available)
- Not based on primary data

Pancreatic enzyme supplements

Formulations available[1]

Brand name (Manufacturer)	Formulation and strength	Product information/Administration information
Creon 10,000 (Solvay)	Capsules	Protease 600 units, lipase 10 000 units, amylase 8000 units. Capsules containing enteric-coated granules. Capsules can be opened, but the granules must not be crushed.
Creon 25,000 (Solvay)	Capsules	Protease 1000 units, lipase 25 000 units, amylase 18 000 units. Capsules containing enteric-coated granules. Capsules can be opened, but the granules must not be crushed.
Creon 40,000 (Solvay)	Capsules	Protease 1600 units, lipase 40 000 units, amylase 25 000 units Capsules containing enteric-coated granules. Capsules can be opened, but the granules must not be crushed.
Creon Micro (Solvay)	Gastro resistant granules	Protease 2000 units, lipase 50 000 units, amylase 36 000 units/g of granules. Granules may be mixed with food and swallowed whole. Not suitable for enteral tube administration.

White & Bradman (2007) Handbook of Drug administration via Enteral feeding tubes

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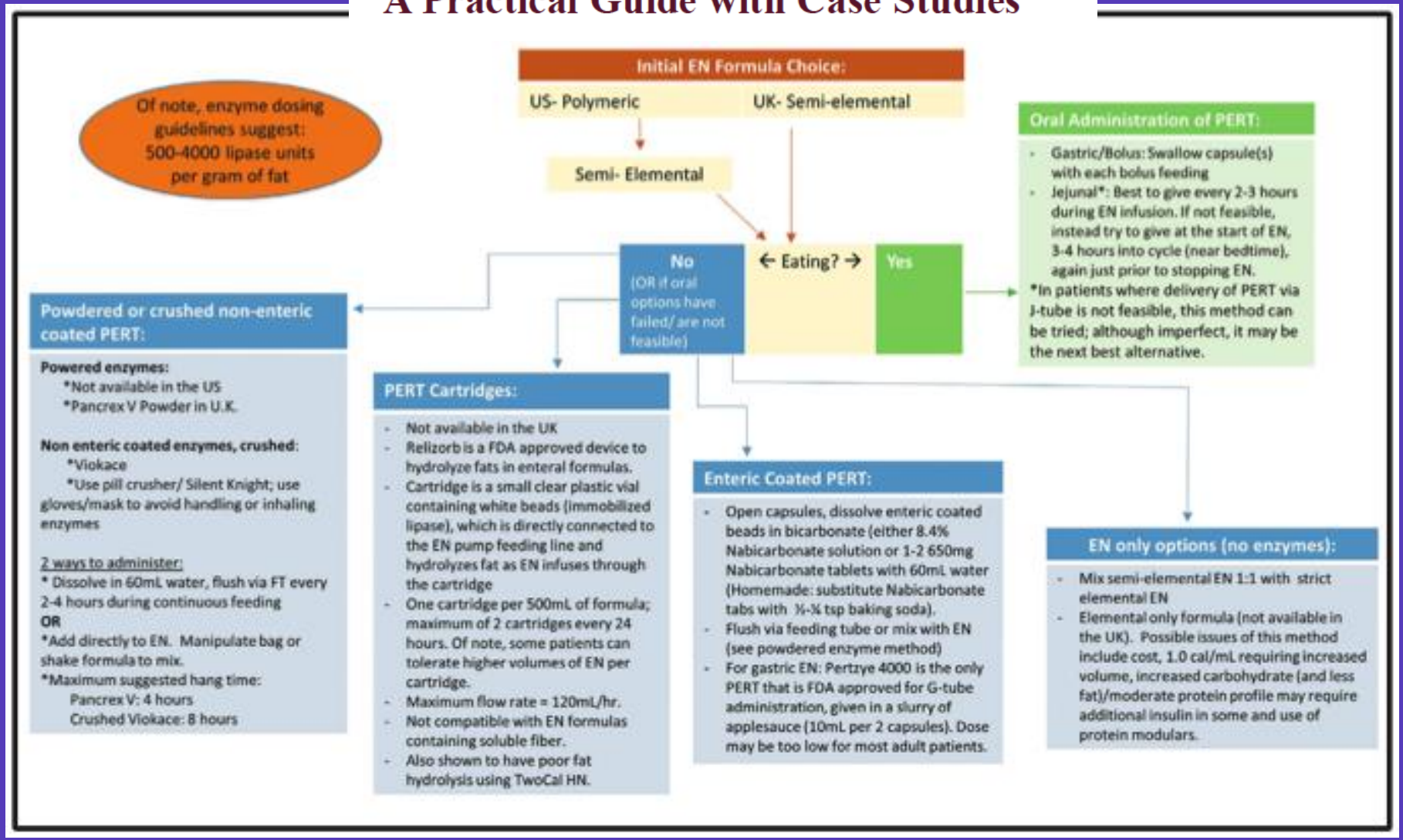
NUTRITION ISSUES IN GASTROENTEROLOGY, SERIES #181

Carol Rees Parrish, M.S., R.D., Series Editor

Pancreatic Exocrine Insufficiency and Enteral Feeding: A Practical Guide with Case Studies



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Study aim

1. To ascertain how enzymes are used alongside enteral feeding in gastric and jejunal feeding tubes

Methodology

- Cross sectional survey
- All health professionals supporting patients with enzymes and enteral feeding in UK
- Gatekeepers: BDA/specialist groups, MDT, colleagues

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Findings

- 3 discrete groups: CF (31%), HPB 24(%), CC (18%)
- 73% from national centre
- Geographical spread (north, south. Wales, Scotland)
- Most trusts didnt have local guidelines (63%)
- Most popular brands: Pancrex & Creon
    - CF - Creon, more specific dosing models
    - HPB/CC- Pancrex, more frequent admin, 2-4hrly, 1g
- Minimal difference between gastric & jejunal administration
- Novel techniques

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Box 2 Administration of PERT with enteral feeds

Powdered enzymes and feeding tubes
NB. Once mixed, use all products immediately. Do not leave to stand
Giving PERT as flushes: mix 1 g scoop pancreatin powder (Pancrex V Powder, Essential Pharmaceuticals, UK) with 50 mL sterile water. Shake well and immediately flush via a feeding tube. Do not give with other medication. Do not flush between the feed and the enzyme as this will reduce the mixing of the feed with the PERT. Administer every 2 hours hours throughout enteral feeding, increase dose of PERT if needed.
Mixing PERT with feed: add 1–2 g Pancrex V Powder directly to the feed in a feeding reservoir. Shake well. Hang straight away and for 4 hours hours only, increase dose of PERT if needed. (NB. Some feeds congeal when PERT is added - discuss with a tertiary centre dietitian prior to adding PERT to feed)
Flushing granules/mini-microspheres via large bore tubes (>CH20): mix with an acidic juice (such as Fortijuce (Nutricia Clinical Care, UK); Ensure Plus Juce (Abbott Nutrition, UK); Fresubin Jucy Drink (Fresenius Kabi, UK)) and flush via the feeding tube every 2 hours hours throughout enteral feeding, increase dose of PERT if needed

PERT, pancreatic enzyme replacement therapy

Phillips et al 2021

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Conclusions

- PEI is often under recognised and under treated
- PERT is often under utilised
- PEI is progressive, and PERT needs monitoring/altering
- PERT alongside enteral feeding is challenging
- More data is needed to assess the effectiveness of PERT methods alongside enteral feeding

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Questions?