Pancreatic exocrine insufficiency and pancreatic enzyme replacement therapy

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Declaration of interests: Honoria received for speaking from Mylan, Sanofi, Vitaflo, Nutricia Clinical Care, Abbott Nutrition and Merck.

Introduction: setting the scene

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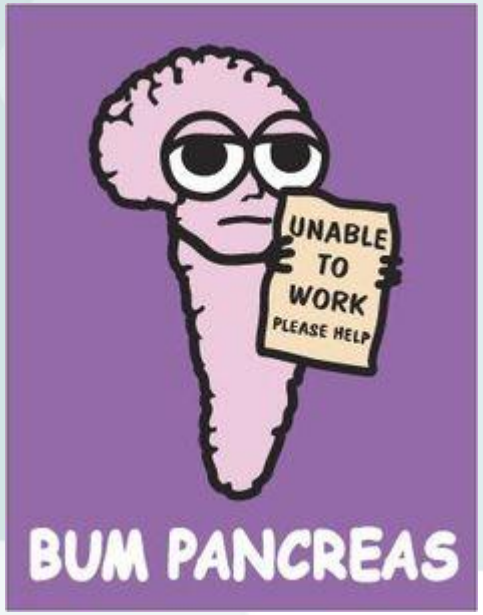

Pancreatic Cancer

- 10,257 new cases of pancreatic cancer per year
- 10th most common cancer in the UK (9th in women [1 in 57]; 12th in men [1 in 53])
- Incidence has increased by 17% since 1990
- 47% of cases are in the over 75's
- 80% of cases are diagnosed in the late stages
- Risk factors: smoking (22% of cases); obesity; alcohol (>3u / day); genetic; chronic pancreatitis; gallstones; diabetes; metabolic syndrome in women only
- 9170 deaths from pancreatic cancer per year
- 5% 10 year survival

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CANCER RESEARCH UK

Introduction

Anatomy and function of the pancreas

Causes and incidence of pancreatic exocrine insufficiency

Impact of pancreatic exocrine insufficiency

Managing pancreatic enzyme replacement therapy

Recommendations for practice

Poll

What is PEI?

1) When the pancreas stops digesting fat
2) When the pancreas stops making insulin
3) When the pancreas is withered / atrophic
4) When the pancreas stops making enough enzymes

Definition

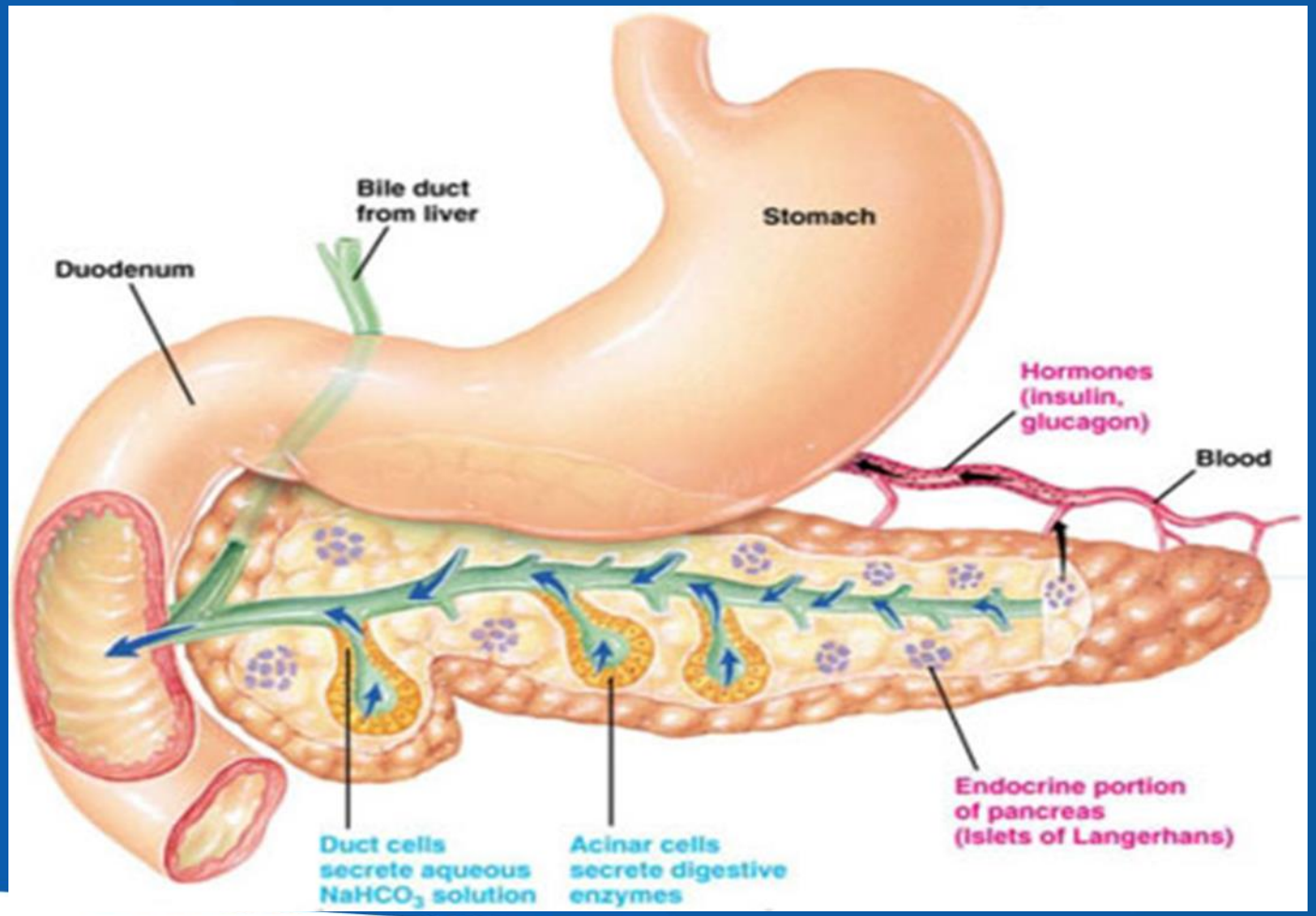
"...deficiency or absence of digestive enzymes leading to maldigestion of food and consequently malabsorption of nutrients" (Whitcomb et al, 2010)

"....pancreas is unable to deliver sufficient amounts of digestive enzymes to the small intestine, leading to maldigestion" (Sikkens et al, 2012)

"Exocrine pancreatic insufficiency results from a progressive loss of acinar pancreatic cells which leads to the secretion of an insufficient amount of digestive enzyme into the duodenum." (Pezzilli et al, 2013)

Failure of the pancreas to secrete sufficient enzymes to achieve normal digestion

Anatomy and function



- Oblong gland 12.5 x 2.5cm
- Consists of endocrine cells: islets of langerhans) which produce glucagon, insulin etc (1% of all cells)
- 99% cells – exocrine function – producing pancreatic enzymes and fluid. (1200-1500mls/day)

Digestive enzymes

Site	Carbohydrate	Fat	Protein
Saliva	Amylase	Salivary lipase	
Gastric Secretion	Gastric Amylase	Gastric Lipase	Pepsin; Rennin; Gelatinase;
Pancreatic Secretion	Amylase	Lipase; Steapsin	Trypsin; Elastase; Chymotrypsin; Carboxypeptidase;
Jejunal / Ileal Secretion	Sucrase; Maltase; Lactase Isomaltase;	Intestinal Lipase	Brush Border Peptidases

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Causes of PEI

- Lack of Healthy Pancreatic Tissue (Primary Insufficiency)
  - Pancreatic Resection - Chronic Pancreatitis
  - Recovering Acute Pancreatitis - Pancreatic Cancer
  - Pancreatic Trauma - Cystic Fibrosis
- Lack of Pancreatic Stimulation (Secondary Insufficiency)
  - Gastric Resection
  - Duodenal Resection
- Some work suggests insufficiency in Coeliac Disease, Diabetes, Irritable bowel syndrome, intensive care, inflammatory bowel disease and the elderly

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Layer et al, 2001

Poll

Which of these is NOT correct?

1. Up to 98% of patients will have PEI after a Whipples
2. More than 50% of people with pancreatic cancer will have PEI on diagnosis
3. People with PEI will always have diarrhoea
4. PEI usually gets worse with time

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How common is PEI in pancreatic cancer?

- Present in the vast majority of people with pancreatic cancer
- Progressive
- 66-94% of patients have PEI at first presentation (all comers)
- Function deteriorates at approximately 10% per month
- Function tests can take 2-6 weeks to give results
- Incidence after surgery depends on the type of operation
  - 20-80% tail of pancreas (distal pancreatectomy)
  - Up to 98% head of pancreas (pancreatico-duodenectomy / Whipple)

Sikkens et al, 2014, Tseng et al, 2016, Phillips et al, 2021, Phillips M, 2015, Okano, 2016

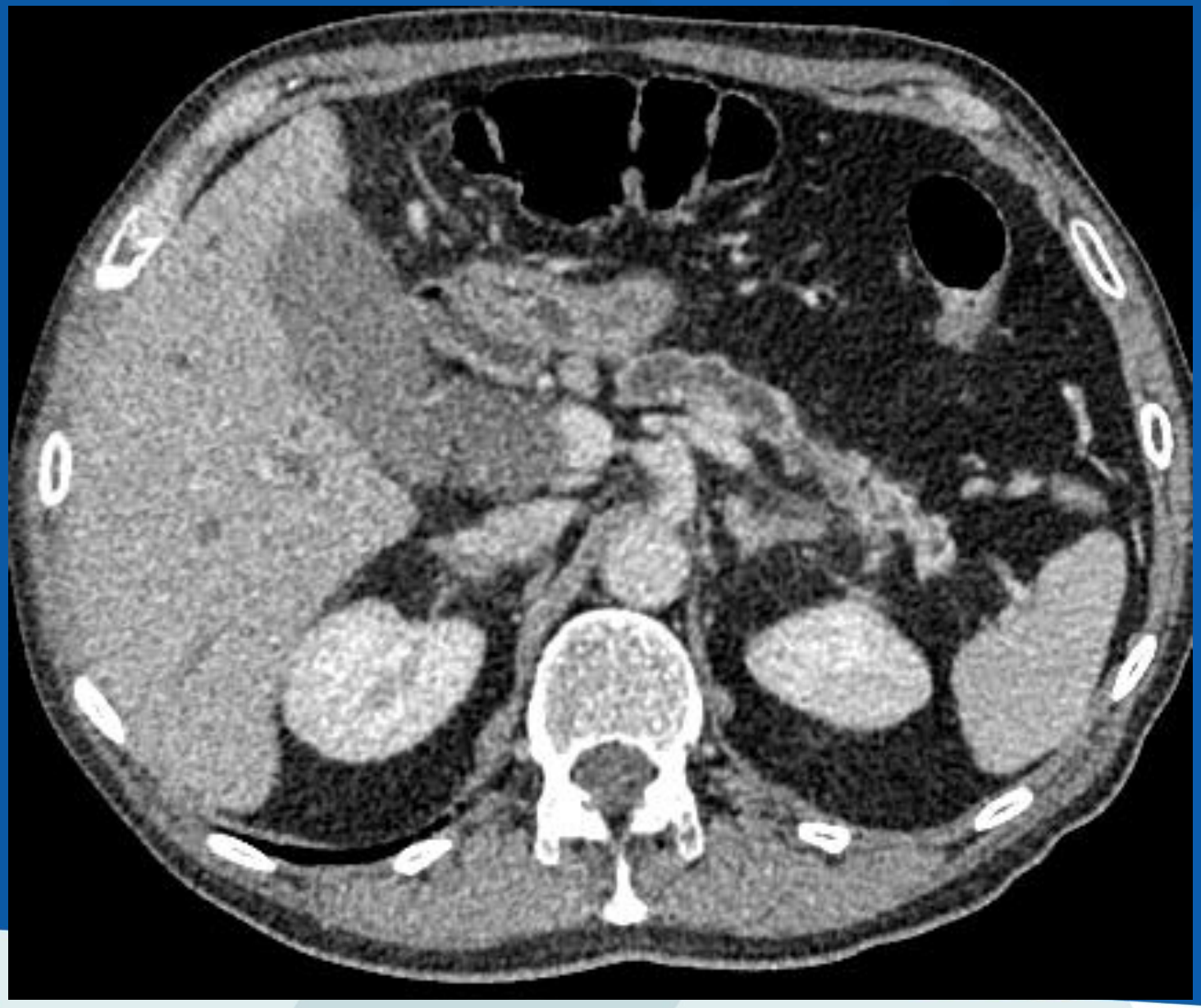
Pancreatic Function Tests

Faecal Elastase

- <200ug/g moderate PEI
- <100ug/g severe PEI
- 200 – 500ug/g (low sensitivity/specificity)
- >500ug/g: Consider age; Dilutional samples (watery / large volume stool); Sample collection technique

Breath tests

Calibre of pancreatic tissue on imaging: Pancreatic ductal dilatation



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Poll

Which of these is NOT a symptom of PEI

1) Bloating

2) Blood sugars that are lower than usual

3) Vitamin and mineral deficiencies

4) Failure to gain weight despite eating really well

5) New diagnosis of diabetes

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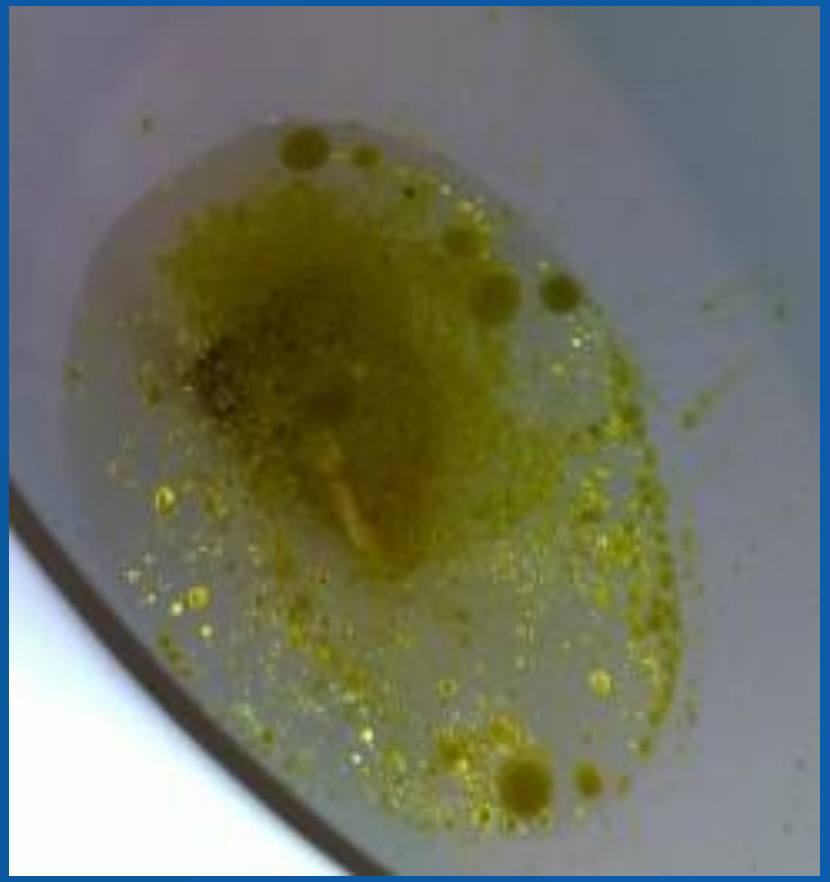
Clinical symptoms (1)

Steatorrhoea

- Loose watery yellow/orange stool
- Floats / difficult to flush away
- Oily / visible food particles

LIMITATIONS

- NOT PRESENT in low fat diet
- MASKED by constipating drugs
- VERY LATE symptom



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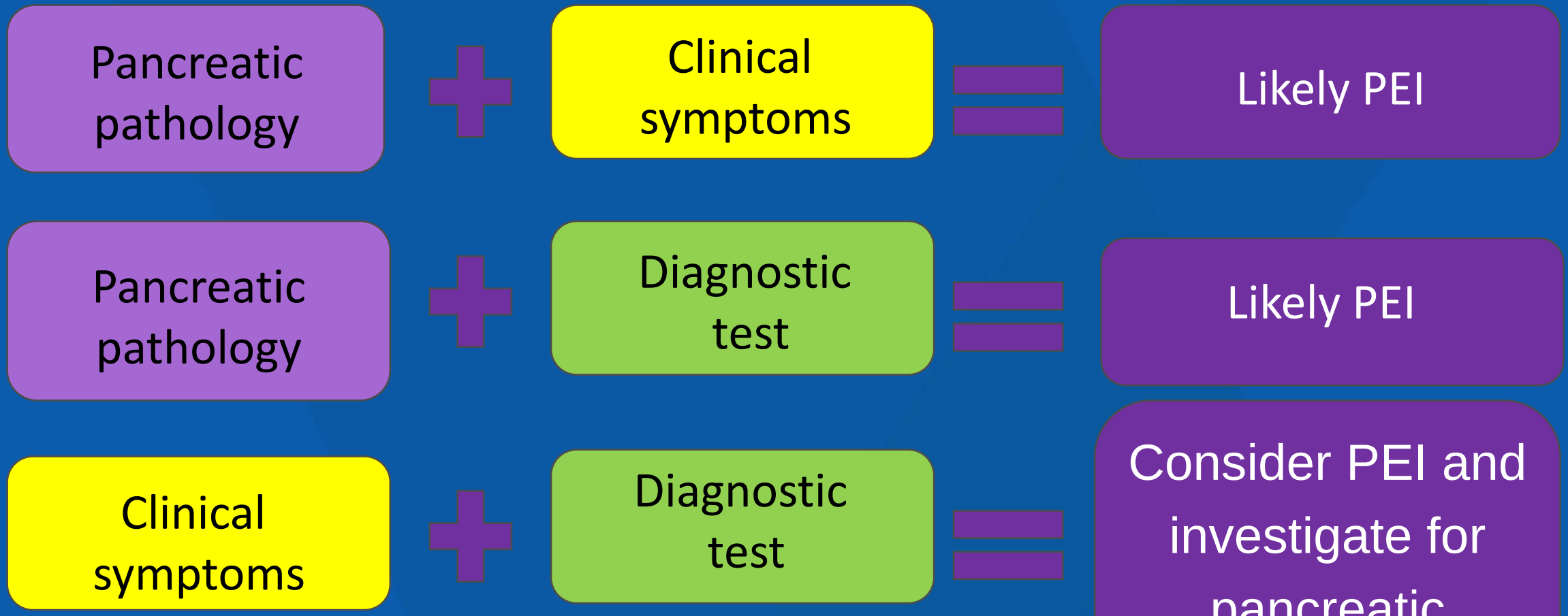
Clinical symptoms (2)

- Large volume stool
- Undigested food in the stool
- Post-prandial abdominal pain
- Nausea / colicky abdominal pain
- Gastro-oesophageal reflux symptoms
- Bloating / flatulence
- *Weight loss despite good oral intake*
- Vitamin deficiencies (especially A,D,E,K,)
- *Hypoglycaemia in patients with diabetes*
  - (O'Keefe et al, 2001, Genova Diagnostics, 2008, Friess & Michalski, 2009)

Diagnosis



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Malignant disease

Survival

- RCT (unresectable ca pancreas)– no benefit; but predominantly tail of pancreas disease (Woo et al, 2016)
- Independently associated with survival in unresectable disease (189 vs. 95 days, retrospective) (Dominguez-Munoz et al, 2018)
- ESPAC studies show the benefit of completing the full chemotherapy regime – performance status….

Pancreatology 19 (2019) 114–121

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

Trial design

Retrospective observational study

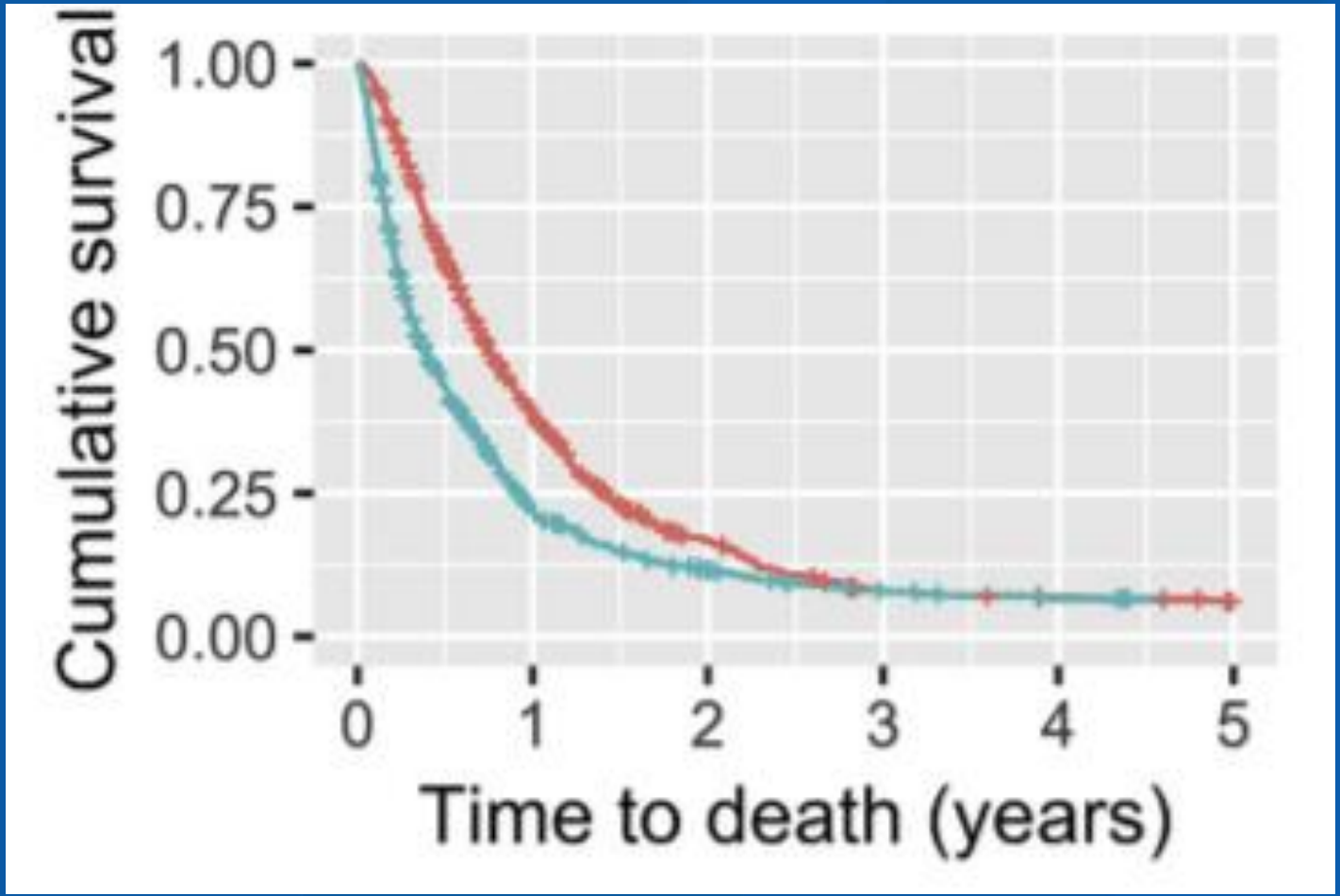
PDAC 1998 – 2015

Excluded those with concurrent pancreatitis, PERT prior to diagnosis

All patients

PERT

Non PERT



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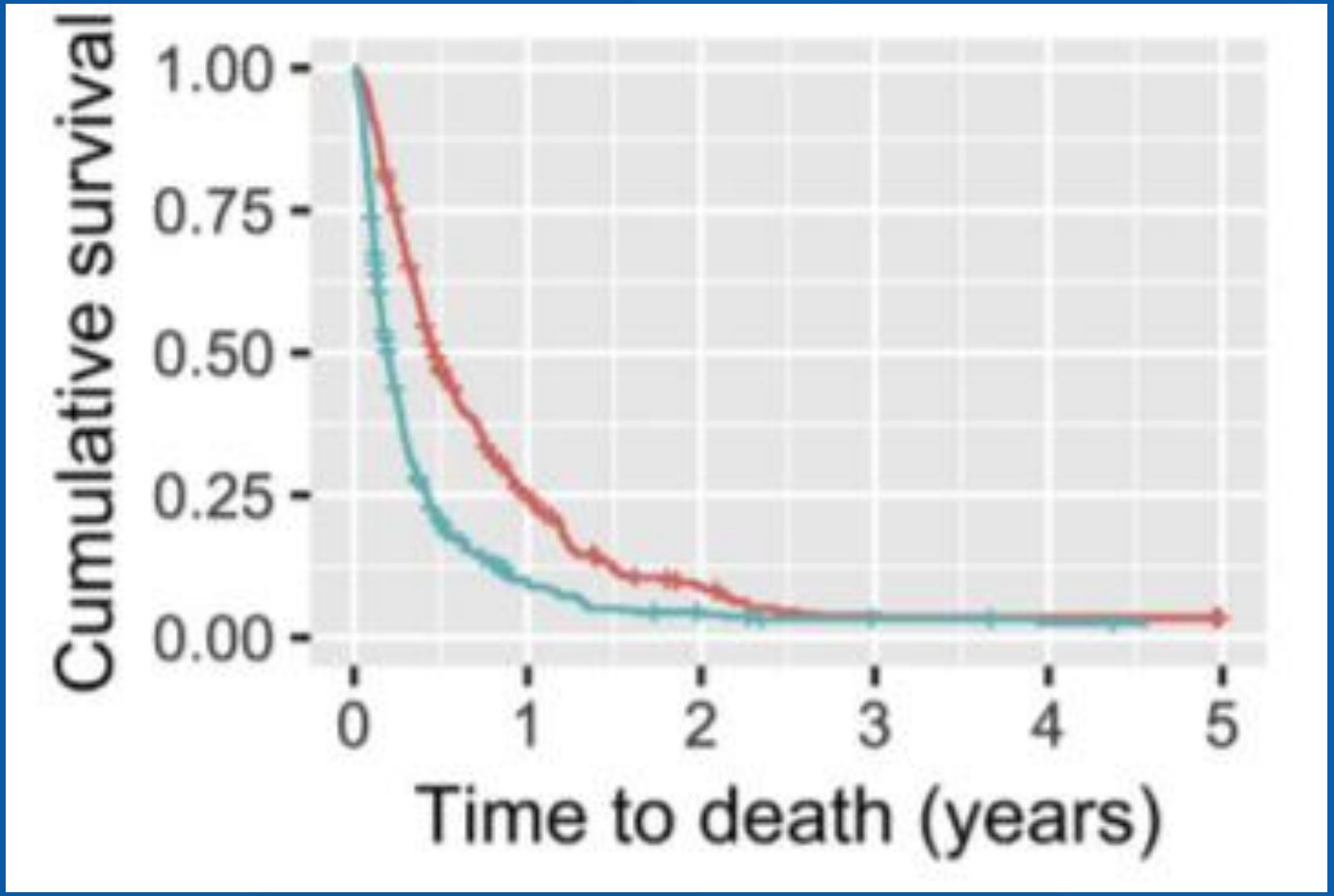
No surgery, no chemo

PERT

Non PERT



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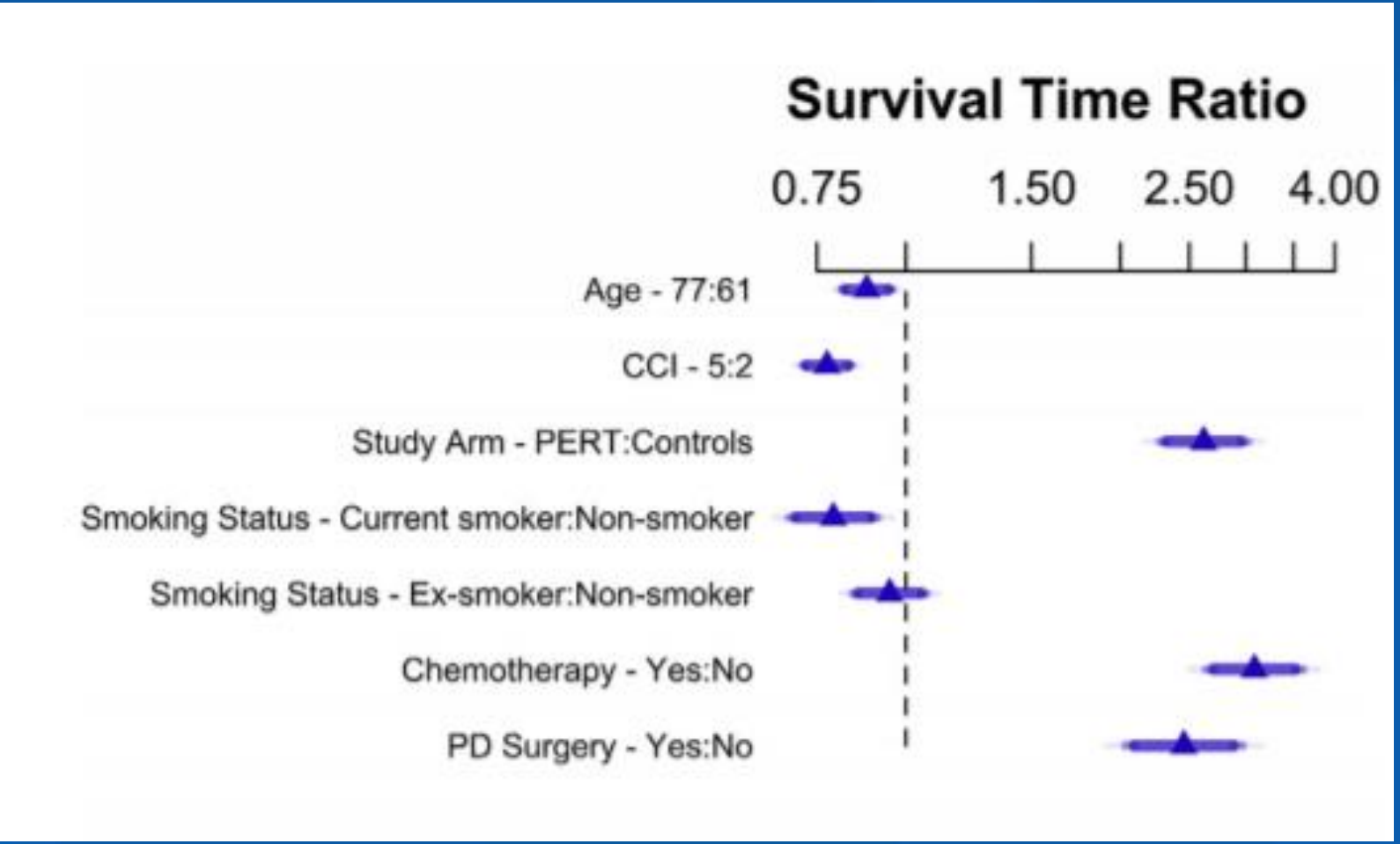
Factors influencing survival



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Study Overview

RICOCHET 1: A National Prospective Audit of the Diagnostic Pathway for Suspected Pancreatic Cancer

<50% patients on PERT

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Richocet study (2021)

- 45% of unresectable patients prescribed PERT
- 74.4% potentially resectable patients prescribed PERT
- 96.9% of pancreatic head resection patients prescribed PERT
- PERT prescription was more likely if:
  - Seen by a dietitian (p = 0.001)
  - Seen in a specialist centre (p= 0.049 – HPB; p=0.009 – pancreas)
  - Seen by a clinical nurse specialist (p = 0.028)

Implications

- 37.5 % of readmissions after pancreatic surgery caused by malnutrition and dehydration (Grewal et al, 2011)
- Sarcopenia independently associated with PEI (Shintakuya et al, 2017)
- “difficulty with digestion” is most common symptom in long term (Cloyd et al, 2017)
- PEI guidance primary unmet need in pancreatic cancer (Gooden & White, 2013)

Sarcopenia and outcome…..

Nutrition 32 (2016) 1231–1237

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

ELSEVIER

Applied nutritional investigation

A high visceral adipose tissue-to-skeletal muscle ratio as a determinant of major complications after pancreatoduodenectomy for cancer

Marta Sandini M.D. [a], Davide P. Bernasconi Ph.D. [b], Davide Fior M.D. [c], Matilde Molinelli M.D. [a], Davide Ippolito M.D. [c], Luca Nespoli M.D. [a], Riccardo Caccialanza M.D. [d], Luca Gianotti M.D., Sc.D. [a,*]

Influence of cachexia and sarcopenia on survival in pancreatic ductal adenocarcinoma: A systematic review

I. Ozola Zalite [a], R. Zykus [b], M. Francisco Gonzalez [c], F. Saygili [d], A. Pukitis [a,e], S. Gaujoux [f,g], R.M. Charnley [h], V. Lyadov [i,*]

CrossMark

Impact of Sarcopenic Obesity on Failure to Rescue from Major Complications Following Pancreaticoduodenectomy for Cancer: Results from a Multicenter Study

Nicolò Pecorelli, MD[1], Giovanni Capretti, MD[2], Marta Sandini, MD[3], Anna Damascelli, MD[4], Giulia Cristel, MD[4], Francesco De Cobelli, MD[4], Luca Gianotti, MD, ScD[3], Alessandro Zerbi, MD[2], and Marco Braga, MD[1]

August 01.

1605-012-1923-5.

Impact of Sarcopenia on Outcomes Following Resection of Pancreatic Adenocarcinoma

Muscle Index

eatic Fistula

Development After Pancreaticoduodenectomy

HIROAKI YAMANE[1], TOMOYUKI ABE[1], HIRONOBU AMANO[1,2], KEIJI HANADA[3], TOMOYUKI MINAMI[3], TSUYOSHI KOBAYASHI[2], TOSHIKATSU FUKUDA[4], SHUJI YONEHARA[5], MASAHIRO NAKAHARA[1], HIDEKI OHDAN[2] and TOSHIO NORIYUKI[1,2]

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UK management

Pancreatic enzyme replacement therapy

- Multiple disease aetiology
- Co-morbidities
- Altered dietary intakes
- Altered meal patterns
- Healthy eating *vs*. nutritional support

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Poll

What is a suitable starting dose for PERT?

1) 5,000 units with meals

2) 10,000 units with meals

3) 22-25,000 units with meals

4) 44-50,000 units with meals

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How do the products compare?

	Amylase	Protease	Lipase
Creon micro (100mg)	3600	200	5000
Pancrex V capsule	9000	460	8000
Creon 10,000	8000	600	10000
Nutrizym 22	19800	1100	22000
Creon 25,000	18000	1000	25000
Pancrease HL	22500	1250	25000
Pancrex V powder (1g)	30000	1400	25000
Creon 40,000	DISCONTINUED		

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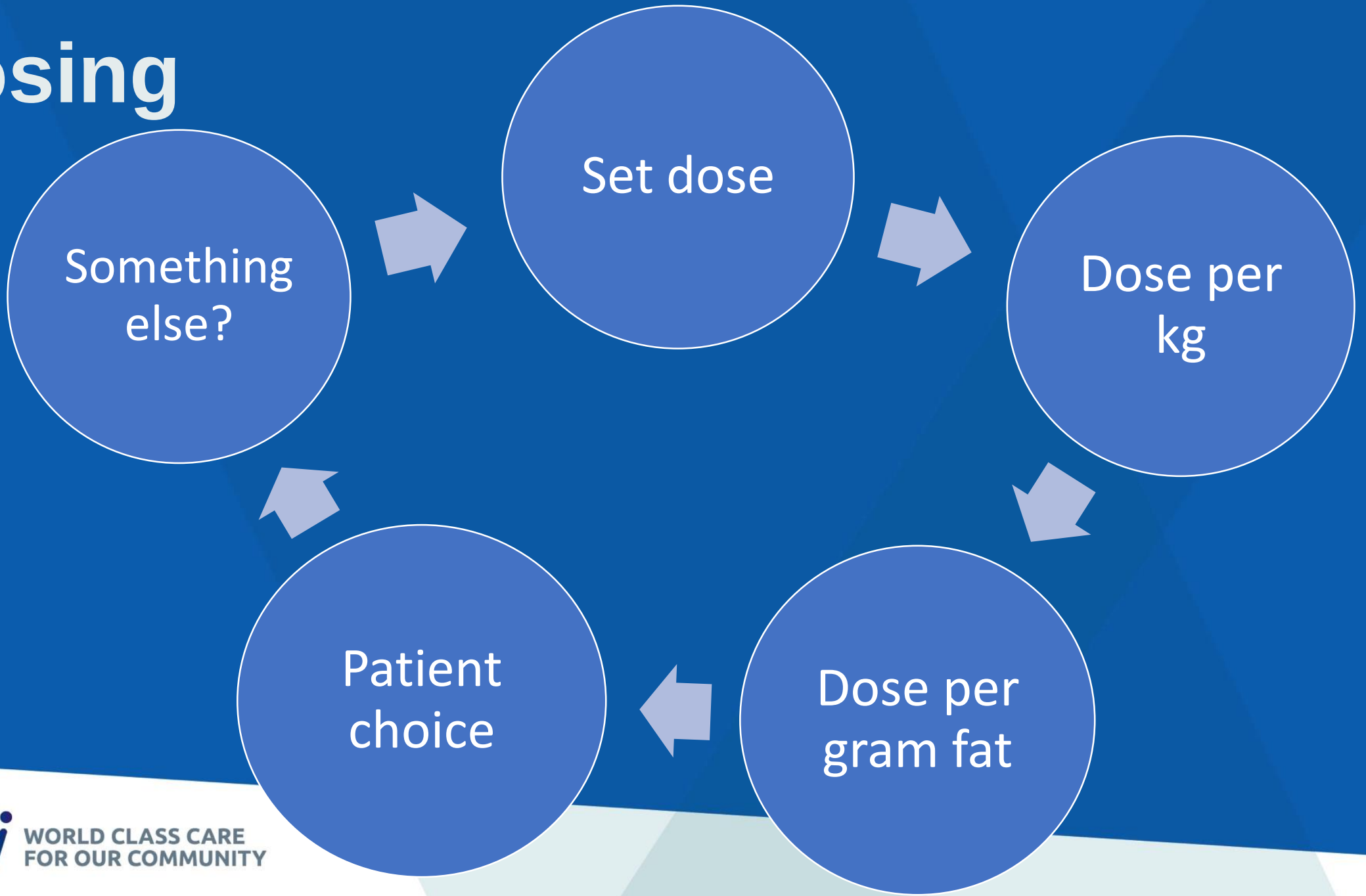
Dosing



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Comparison of weight-based doses of enteric-coated microtablet enzyme preparations in patient with cystic fibrosis

N = 21

Population: Cystic Fibrosis

Open label crossover: 500u/kg with meals and 250U/kg with snacks compared to 1500u/kg with meals and 750u/kg with snacks.

Diet : 100g fat / day

CFA: increased from 86% to 91% ($P<0.05$)

(Beker et al, J.Paed Gastrol Nutr. 1994 Aug;19(2):191-7).

RESEARCH ARTICLE

Clinical validation of an evidence-based method to adjust Pancreatic Enzyme Replacement Therapy through a prospective interventional study in paediatric patients with Cystic Fibrosis

Joaquim Calvo-Lerma[1,2]*, Jessie Hulst[3], Mieke Boon[4], Carla Colombo[5], Etna Masip[1], Mar Ruperto[6], Victoria Fornés-Ferrer[1], Els van der Wiel[3], Ine Claes[4], Maria Garriga[6], Maria Roca[1], Paula Crespo-Escobar[1], Anna Bulfamante[5], Sandra Woodcock[3], Sandra Martínez-Barona[1], Ana Andrés[2], Kris de Boeck[4], Carmen Ribes-Koninckx[1], on behalf of MyCyFAPP project[¶]

PLOS ONE | https://doi.org/10.1371/journal.pone.0213216 March 12, 2019

NHS
Royal Surrey
NHS Foundation Trust

- Multicentre trial
- Cystic fibrosis cohort
- Diet – 40% Lipid; 40% CHO and 20% Protein
- 1622 – 2573kcal/day

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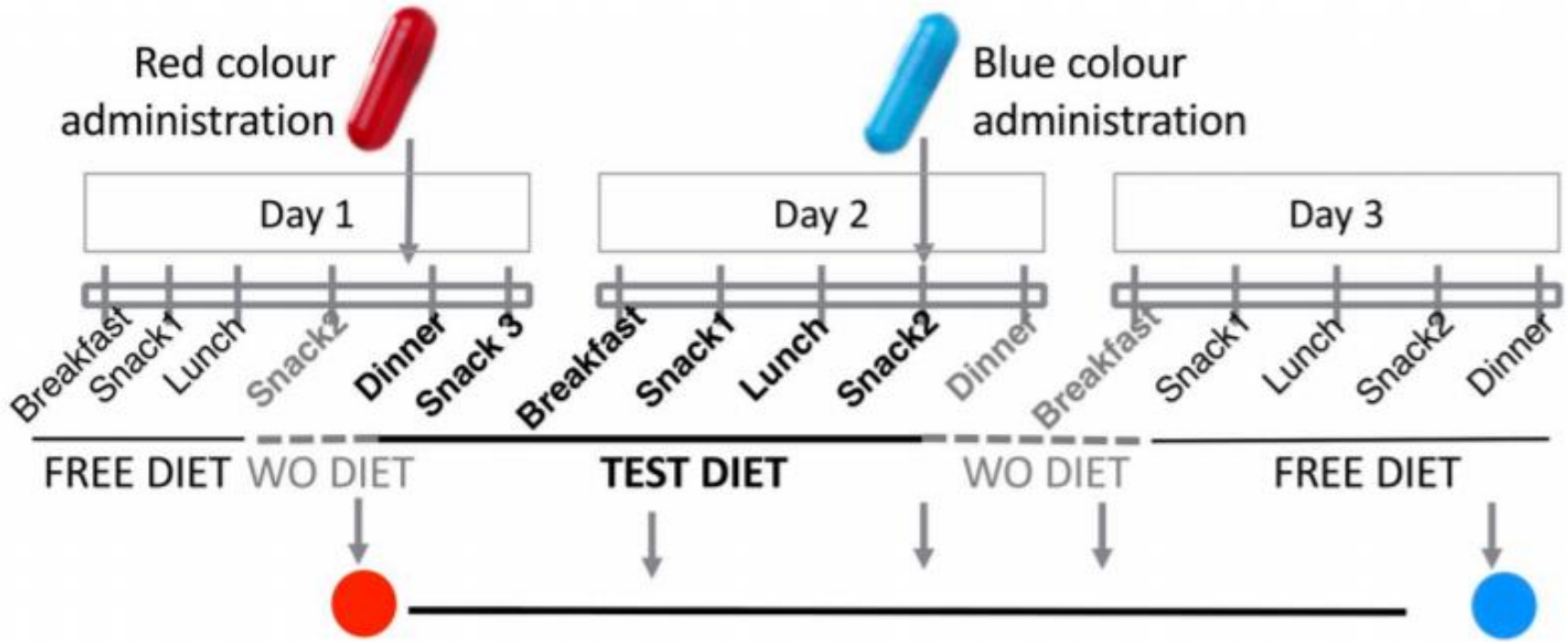

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$$IOD = \frac{g(90\%_{clinical\ target\ CFA}) - \beta_0 - (\beta_1 \cdot transit\ time) - (\beta_3 \cdot age) - (\beta_4 \cdot PPI\ intake)}{\beta_2}$$

Table 3. Beta regression model to assess the influence of the study variables on CFA, including the dose of enzymes (TOD) and the individual factors intake of proton pump inhibitors (PPI), age and transit time.

	(exp)Estimate	Confidence Interval CI 95%	p-value
(Intercept) (β_0)	2.839	[0.223, 36.147]	0.42
TOD (β_2)	0.999	[0.998, 1.000]	0.13
PPI intake (β_4)	1.367	[0.885, 2.115]	0.09
Age (β_3)	1.013	[0.961, 1.069]	0.62
Transit time (β_1)	1.815	[1.177, 2.797]	0.007

Transit time played a significant role in results: longer the transit time the greater the CFA

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Table 1. Theoretical optimal doses of enzymatic supplement (TOD) expressed in lipase units per gram of fat (LU/g fat) for a selection of eight foods previously determined by means of an in vitro digestion model. Combination of the foods conformed the meals used in the study protocol in order to assess the efficacy of the TOD assigned to each food.

Test meal	Fat content (g/ 100g)	Theoretical optimal dose of enzymes (TOD) (LU/ g fat)	Portion size (g) per test diet level (L[a])	Fixed dose of enzymatic supplement based on TOD (total LU)
Salad with olive oil	10	1613	L1: 70	11291
			L2: 100	16130
			L3: 100	16130
			L4: 150	24195
Ham & cheese Pizza	8.3	1375	L1: 170	19401
			L2: 220	25107
			L3: 220	25107
			L4: 250	28531
Yoghurt	10	1240	L1: 125	15500
			L2: 125	15500
			L3: 125	15500
			L4: 125	15500
Ham & cheese Sandwich	10.2	1660	L1: 110	18625
			L2: 130	22011
			L3: 140	23704
			L4: 140	23704
Milk	3.6	1480	L1: 200	10656
			L2: 200	10656
			L3: 250	13320
			L4: 250	13320

- Not validated in free diet
- Complex equation requiring assessment of transit time
- Transit time changes: opiates; laxatives; changes in hydration / diet
- ? Applicable to real life?
- ? Gives a baseline?

And it is not just fat….

Medium-Chain Triglyceride Absorption in Patients with Pancreatic Insufficiency

S. CALIARI, L. BENINI, C. SEMBENINI, B. GREGORI, V. CARNIELLI & I. VANTINI
Division of Gastroenterologic Rehabilitation, University of Verona, Verona, and Dept. of Pediatrics, University of Padua, Padua, Italy

4 way Crossover trial: LCT vs. MCT +/- 50,000 units lipase
N= 6, all male Chronic Pancreatitis patients
All had severe exocrine insufficiency (CFA < 80%)
(1 x distal panc, 1 x total gastrectomy, 1 x distal gastrectomy, 1x whipple, 2 on insulin.)

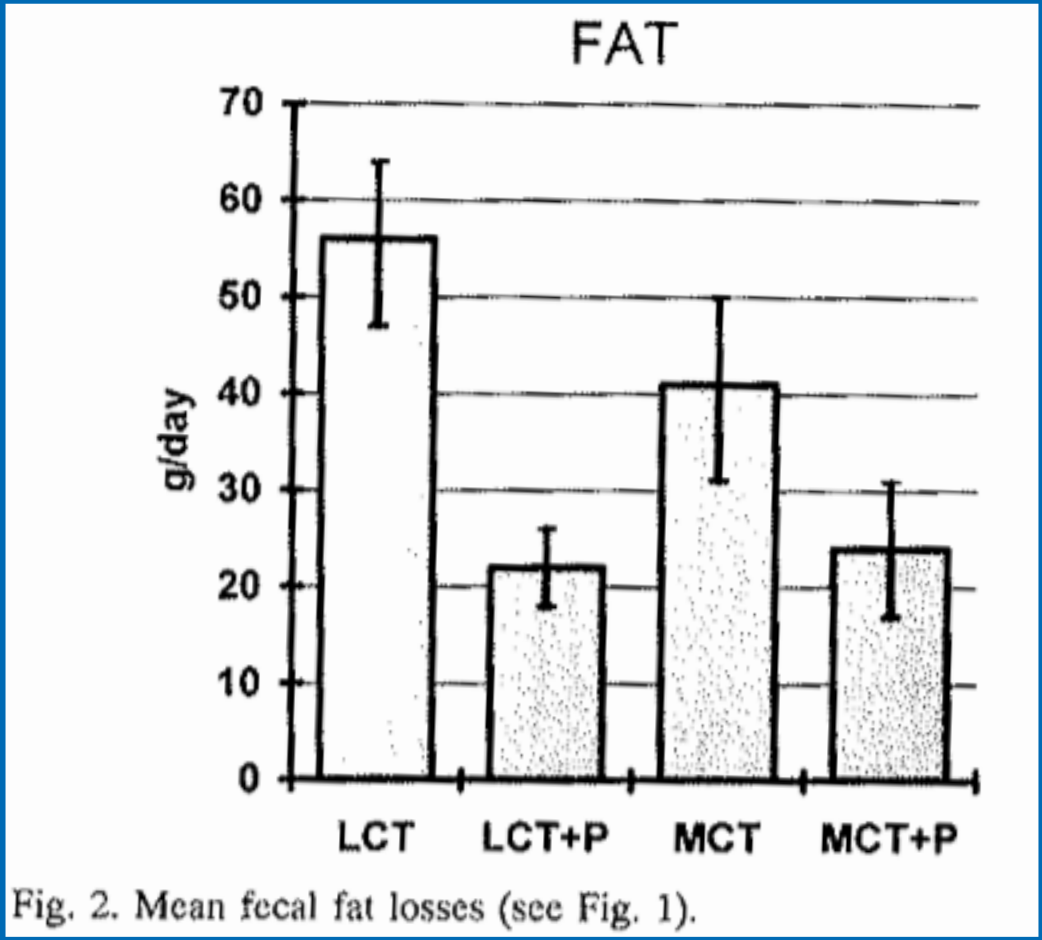

Fig. 2. Mean fecal fat losses (see Fig. 1).

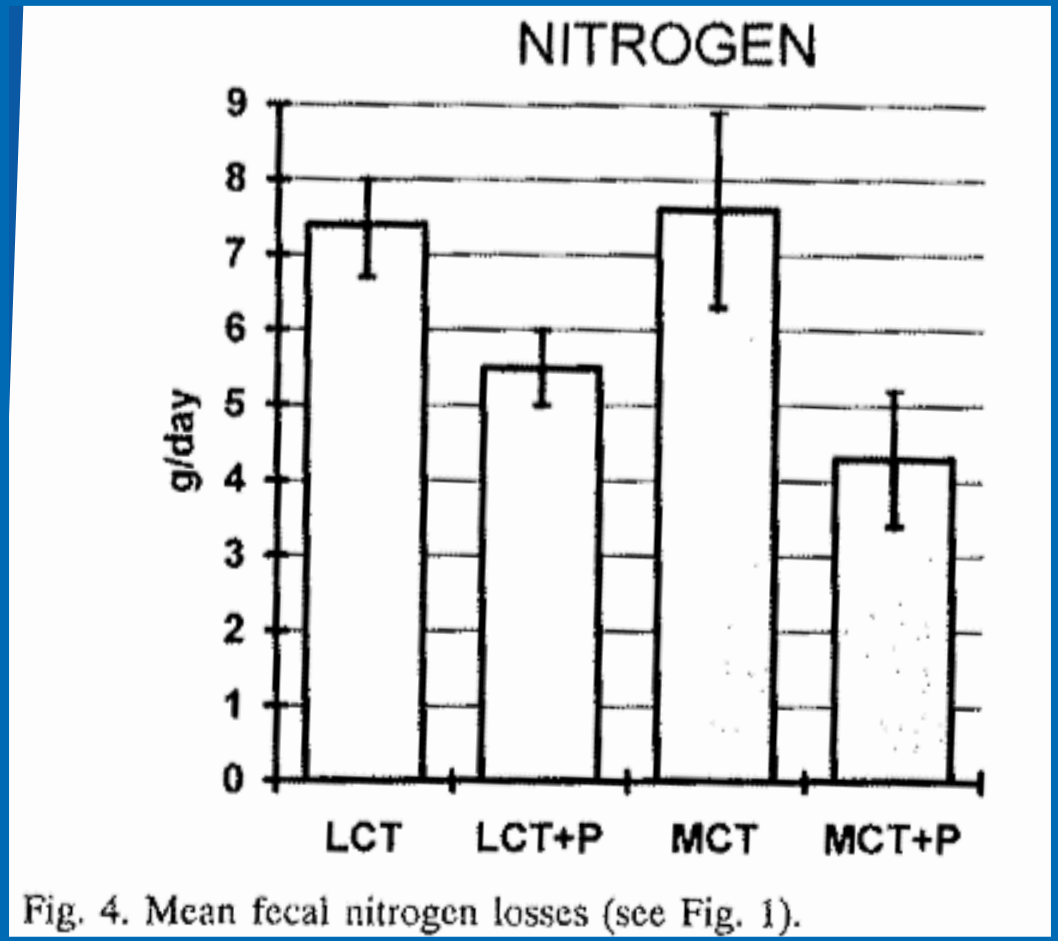

Fig. 4. Mean fecal nitrogen losses (see Fig. 1).

Caliari et al, 1996

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Dosing used in clinical trials

Study	Cohort	Dose	Benefit
Kim et al, Clin Gastroenterol Hepatol. 2019	RCT n=304 Pancreatico-duodenectomy	40,000 units lipase with meals	Increase body weight; increased pre-albumin
Sato et al, Pancreas. 2018 Aug;47(7):800-806	N=88 PDAC chemotherapy	48,000 units lipase with meals	No difference in nutritional markers in 8/52 trial Survival 19/12 *vs*. 12/12 (p=0.07)
Woo et al, Pancreatology. 2016 Nov - Dec;16(6):1099-1105	N= 67 Unresectable PDAC	25,000 capsules x 6-9 per day	NO difference in nutritional markers or QOL in 8/52 trial
Bruno et al, Gut. 1998 Jan;42(1):92-6	N = 21 Unresectable PDAC	50,000 units lipase with meals; 25,000 units with snacks	12% improvement in CFA; weight gain in intervention; weight loss in placebo

Recommended dose

STARTING DOSE....

44 - 50,000 units with meals

22 - 25,000 units with snacks

25 - 50,000 units with supplements

Will need higher dose with larger meals

Increase until symptom control

Poll

Which of these do you NOT need to take PERT with?

1) Cup of tea and two bourbon biscuits

2) Mug of peppermint tea

3) Milkshake

4) Cup of milky coffee

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NICE National Institute for Health and Care Excellence

NICE guideline

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.

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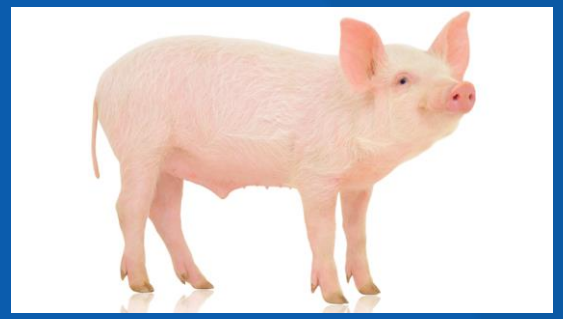
Recommendations for clinical practice

CONSENT



Timing

- Mix with food
- Allow for slow meals / multiple courses / gastric emptying

Dose

- Minimum starting dose 50,000u with meals; 25,000u with snacks
- Increase until symptoms are under control
- Snacks *vs*. meals
- Nutritional supplements

Prevent denaturation

- <25^{o}C
- ?Proton pump inhibitor?
- Avoid swallowing with hot food/fluids

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Contra-indications

For Pancrease HL®

Should not be used in children aged 15 years or less with cystic fibrosis

For Nutrizym 22® gastro-resistant capsules

Should not be used in children aged 15 years or less with cystic fibrosis

Cautions

Can irritate the perioral skin and buccal mucosa if retained in the mouth; excessive doses can cause perianal irritation

Side-effects

Common or very common

Abdominal distension; constipation; nausea; vomiting

Uncommon

Skin reactions

Frequency not known

Fibrosing colonopathy

Contraindications and side effects

- **CONTRAINDICATIONS**
  - CONSENT: Porcine content
  - Pork allergy / previous intolerance
- **SIDE EFFECTS**
  - Nausea
  - Gout (uric acid)
  - Fibrosing colonopathy
- **PREGNANCY & BREASTFEEDING:**
  - Essential fatty acids are needed for brain and retinol development in the first 8 weeks of pregnancy – DO NOT STOP PERT

What do you NEED to know: PEI and PERT

- Exocrine insufficiency is progressive and doses escalate with time
- Some patients need really high doses (>150,000 units with a meal = >25 capsules / day = 9-10 x 100 cap tubs per month)
- Significant pill burden
- Micronutrient deficiency common
- Enzymes denatured by excess temperature and acid
- Treat like insulin – different doses for different patients for different meals

Conclusion

- PEI is under recognised
- Many patients are on sub-optimal doses
- Appropriate therapy improves outcome
- Multiple factors play a role in dose adjustment – individual management
- Permission to dose escalate
- More data needed to explore relationship with survival in pancreatic cancer.