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NHS Foundation Trust

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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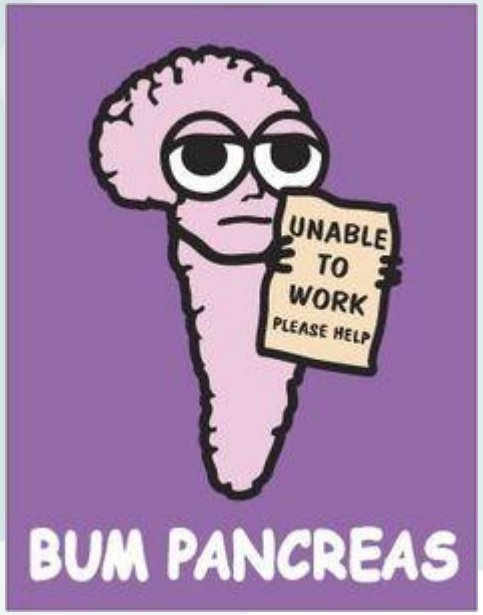

Introduction

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

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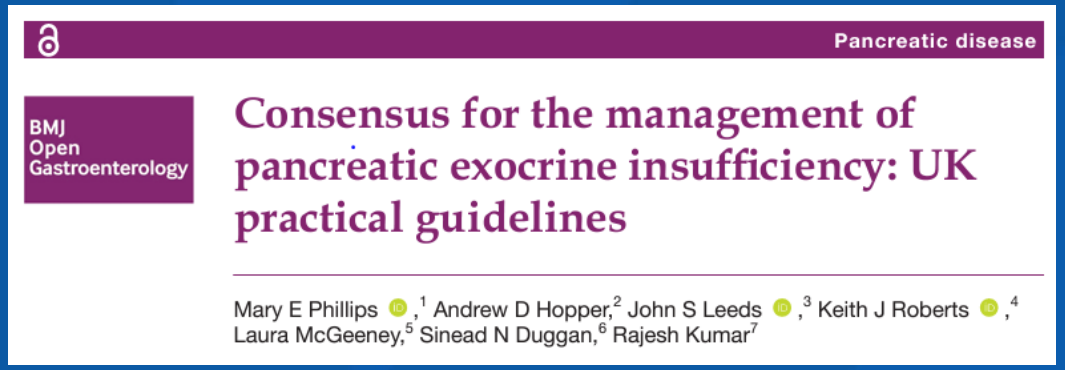
Definition



Definition and diagnosis of PEI

Statement 1.1: PEI is defined as a reduction of pancreatic exocrine activity in the intestine at a level that prevents normal digestion (grade 1C; 100% agreement)

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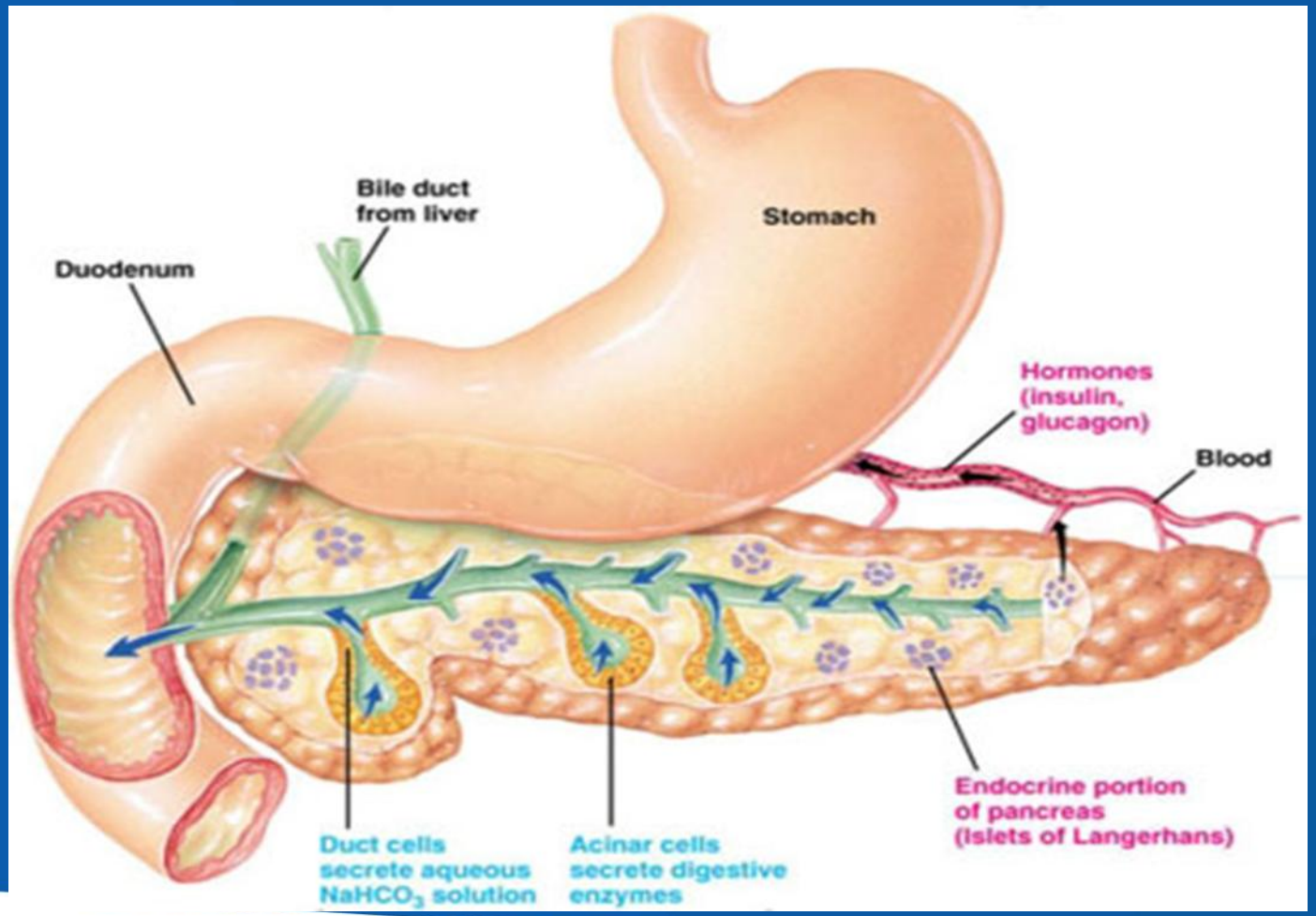
Anatomy and function



- 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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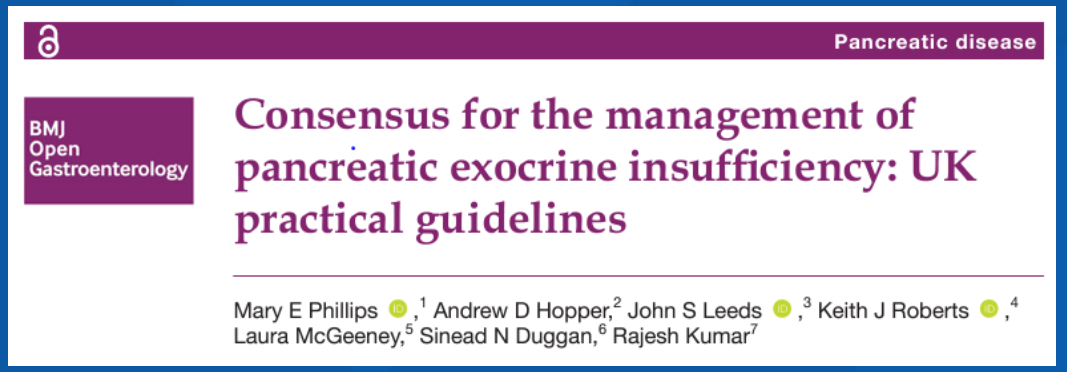

Pancreatic disease

BMJ Open Gastroenterology

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

Mary E Phillips [1], Andrew D Hopper [2], John S Leeds [3], Keith J Roberts [4], Laura McGeeney [5], Sinead N Duggan [6], Rajesh Kumar [7]

Definition and diagnosis of PEI

Statement 1.1: PEI is defined as a reduction of pancreatic exocrine activity in the intestine at a level that prevents normal digestion (grade 1C; 100% agreement)

Primary PEI: Lack of pancreatic secretion (cancer, pancreatitis, resection)

Secondary PEI: Lack of pancreatic stimulation (gastric resection /duodenal bypass)

Others – small bowel disease, enterokinase deficiency, endocrine failure

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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

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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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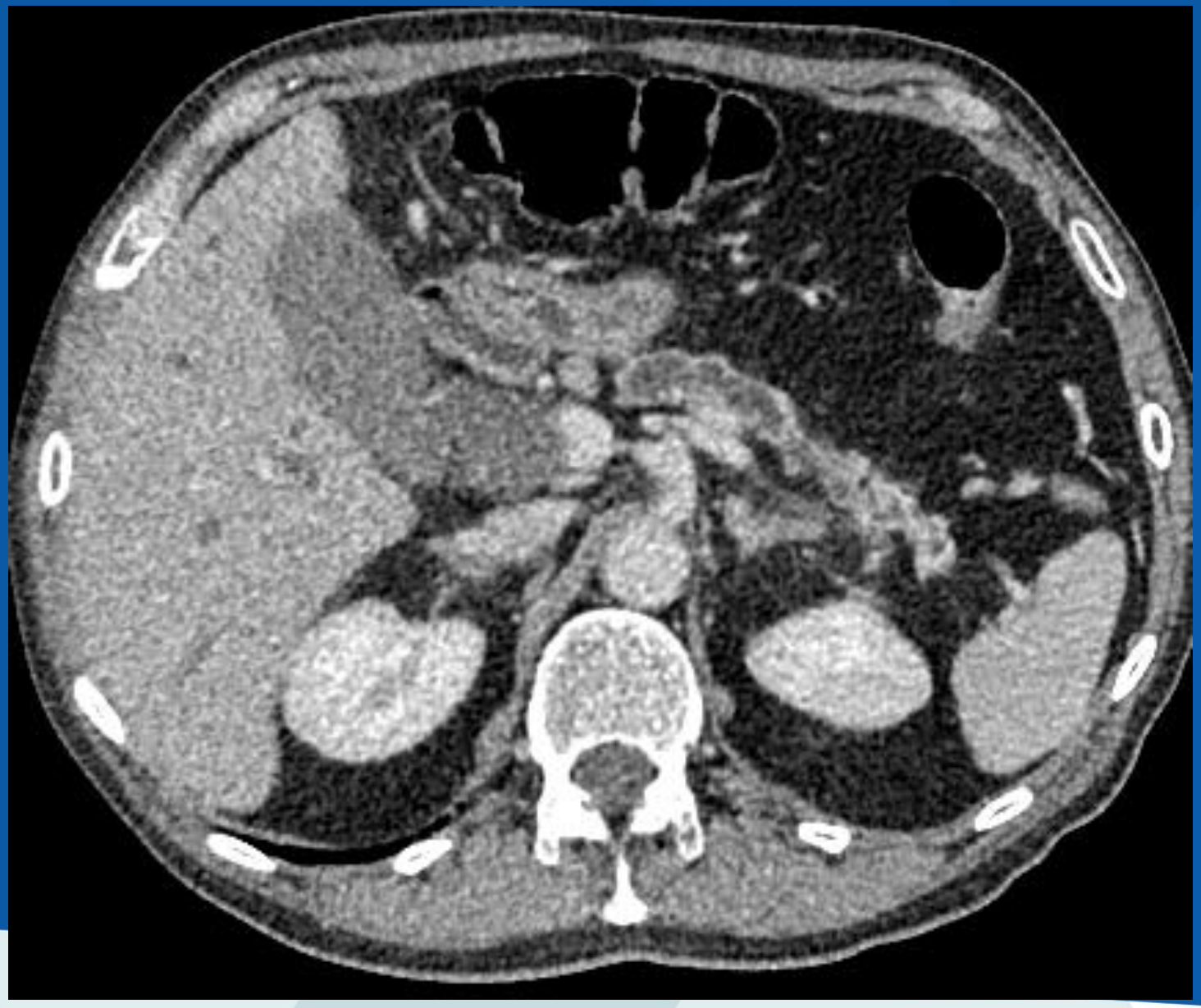

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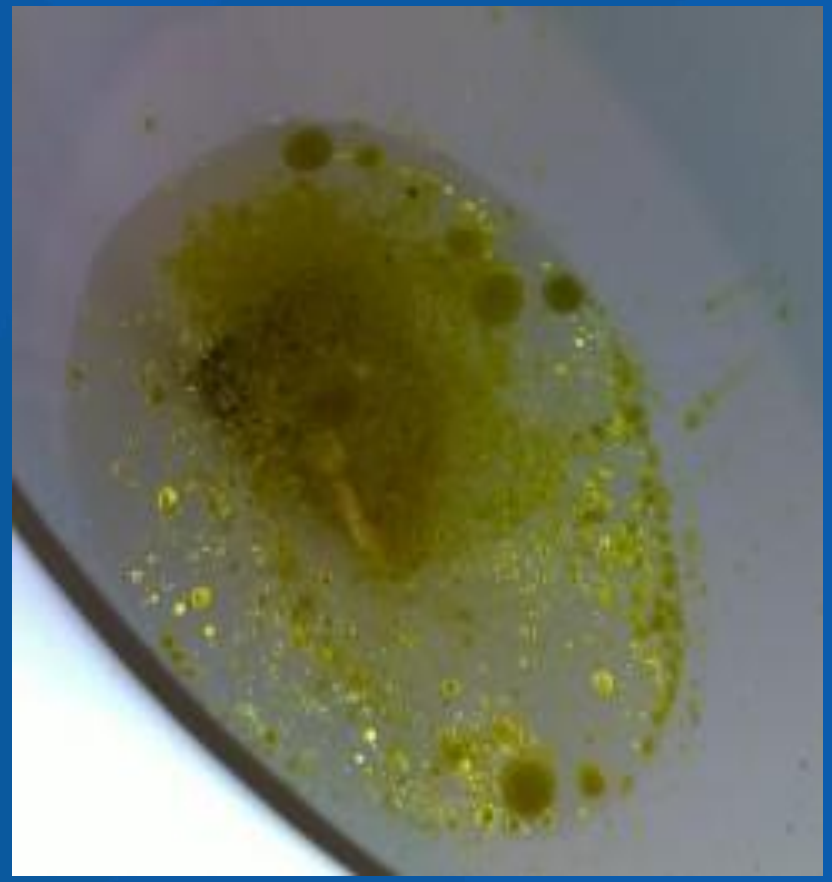
Clinical symptoms (1)

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 – only present in 14% cases



Midha et al, 2008

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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

Pancreatic pathology	+	Clinical symptoms	=	Likely PEI
Pancreatic pathology	+	Diagnostic test	=	Likely PEI
Clinical symptoms	+	Diagnostic test	=	Consider PEI and investigate for pancreatic pathology

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Malignant disease

Survival

- RCT (unresectable ca pancreas)– no benefit; but predominantly tail of pancreas disease (Woo et al, 2016)
- Survival benefit(Dominguez-Munoz et al, 2018, Roberts, 2019)
- 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

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Trial design

Retrospective observational study

PDAC 1998 – 2015

Excluded those with concurrent pancreatitis, PERT prior to diagnosis

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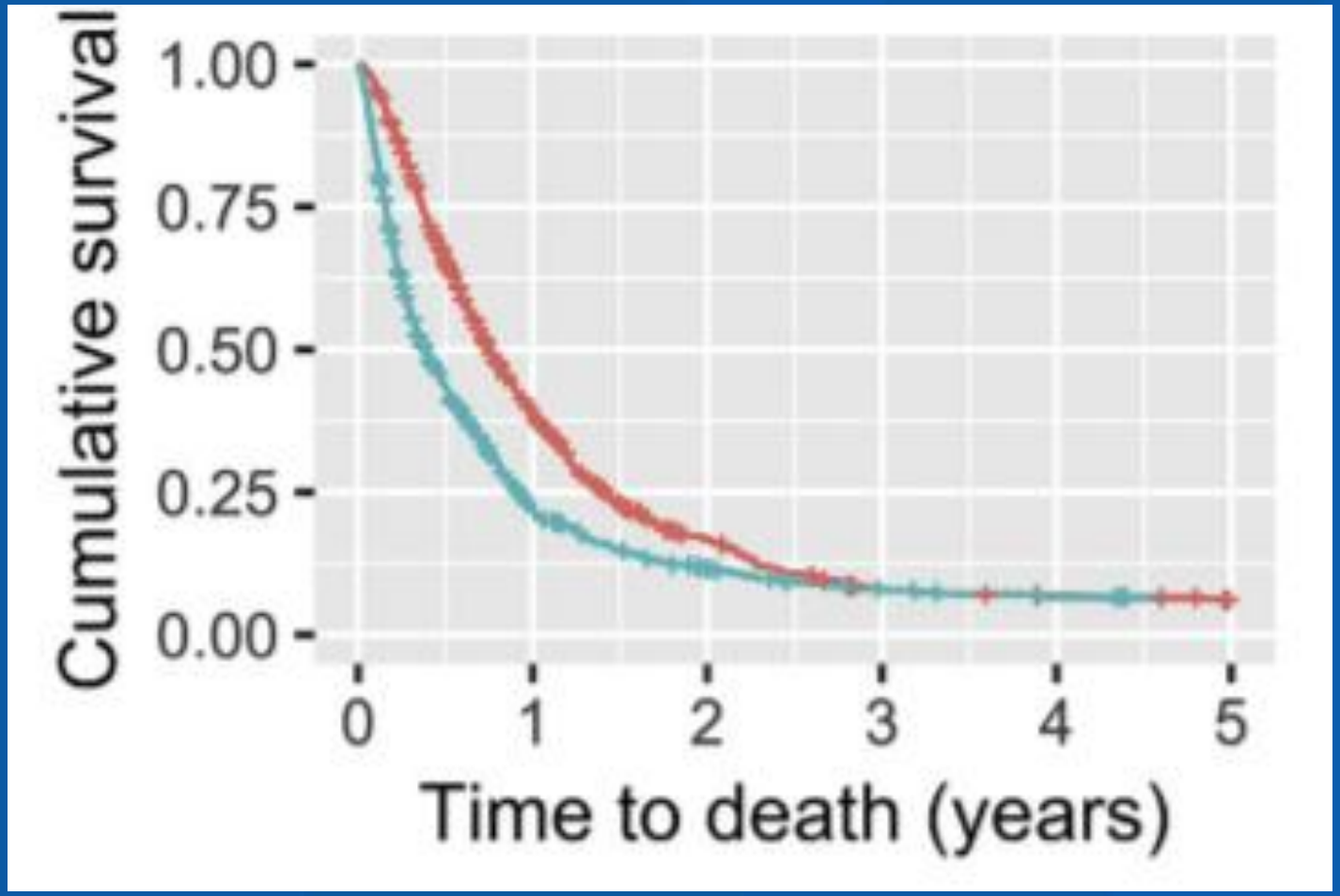
All patients

PERT

Non PERT



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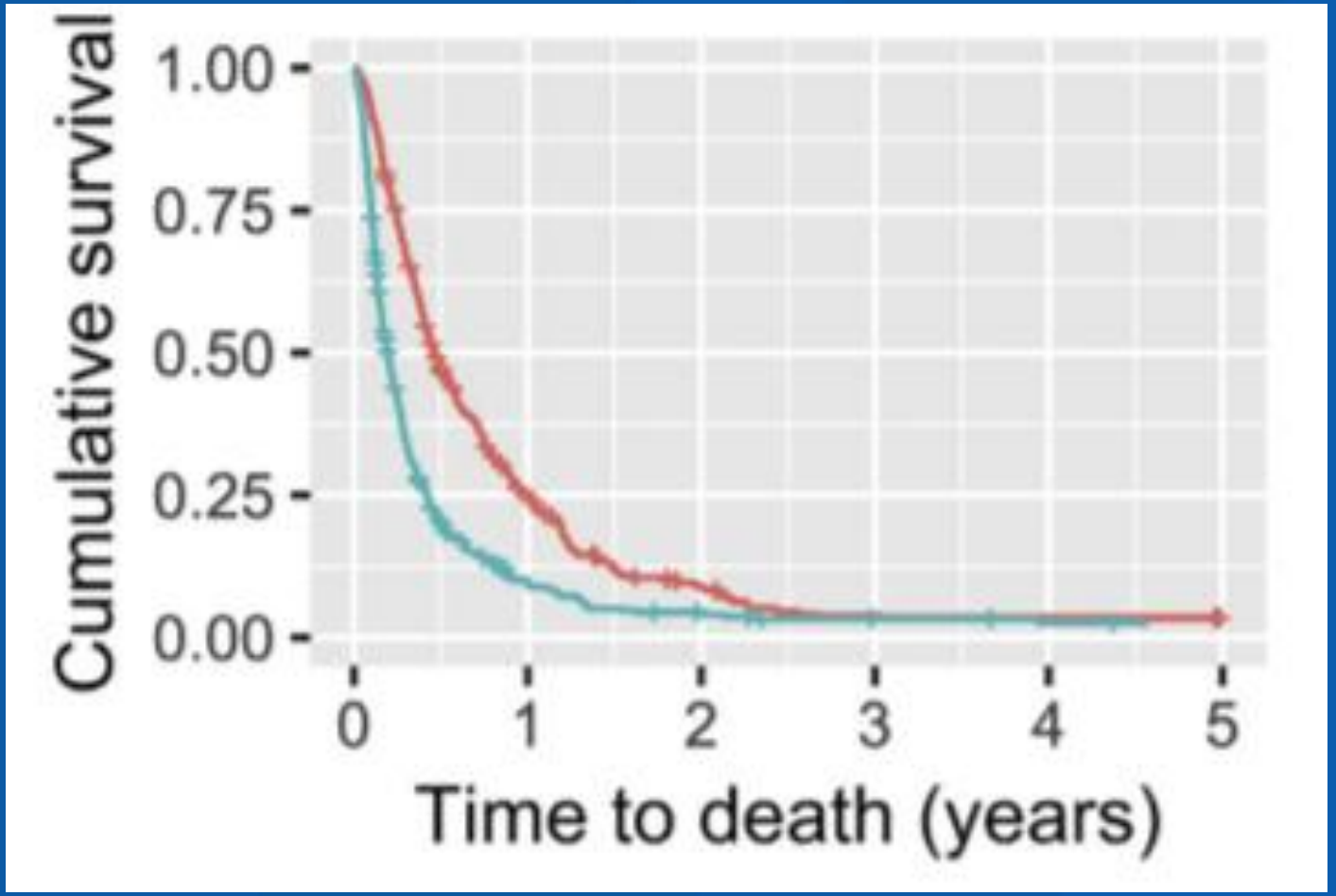
No surgery, no chemo

PERT

Non PERT



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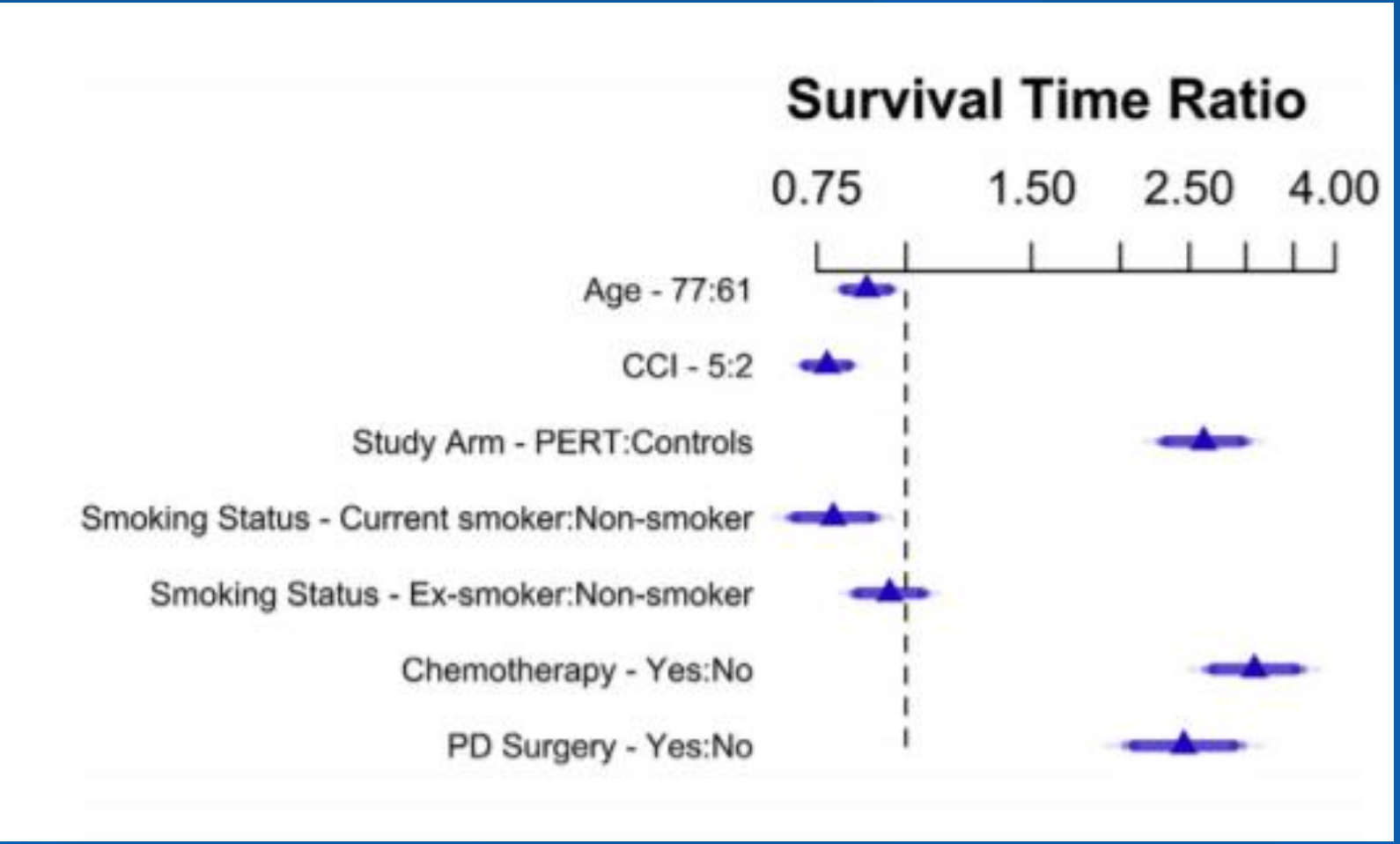
Factors influencing survival



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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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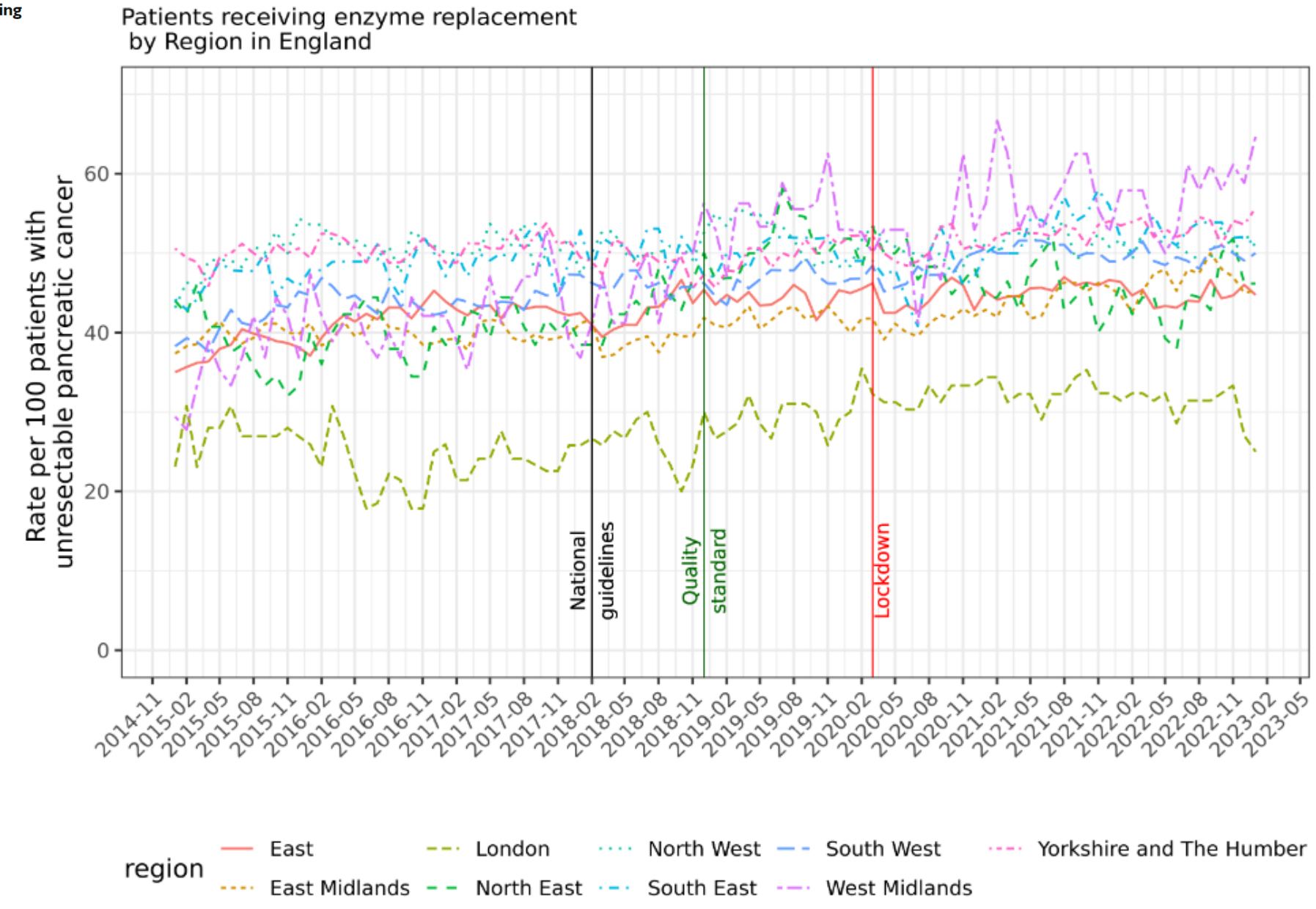
Ricochet study (2021)

- 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)

The impact of the COVID-19 pandemic on prescribing of pancreatic enzyme replacement therapy for people with unresectable pancreatic cancer in England.A cohort study using OpenSafely-TPP

Agnieszka Lemanska, Colm Andrews, Louis Fisher, Ben Butler-Cole, Amir Mehrkar, Keith J Roberts, Ben Goldacre, Alex J Walker, The OpenSAFELY Collaborative, Brian MacKenna

doi: https://doi.org/10.1101/2022.07.08.22277317



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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)

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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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How do the products compare?

	Amylase	Protease	Lipase
Creon micro (100mg)	3600	200	5000
Pancrex V capsule (340mg)	9000	460	8000
Creon 10,000	8000	600	10000
Nutrizym 22	19800	1100	22000
Creon 25,000	18000	1000	25000
Pancrease HL	DISCONTINUED		
Pancrex V powder (1g)	30000	1400	25000
Creon 40,000	DISCONTINUED		

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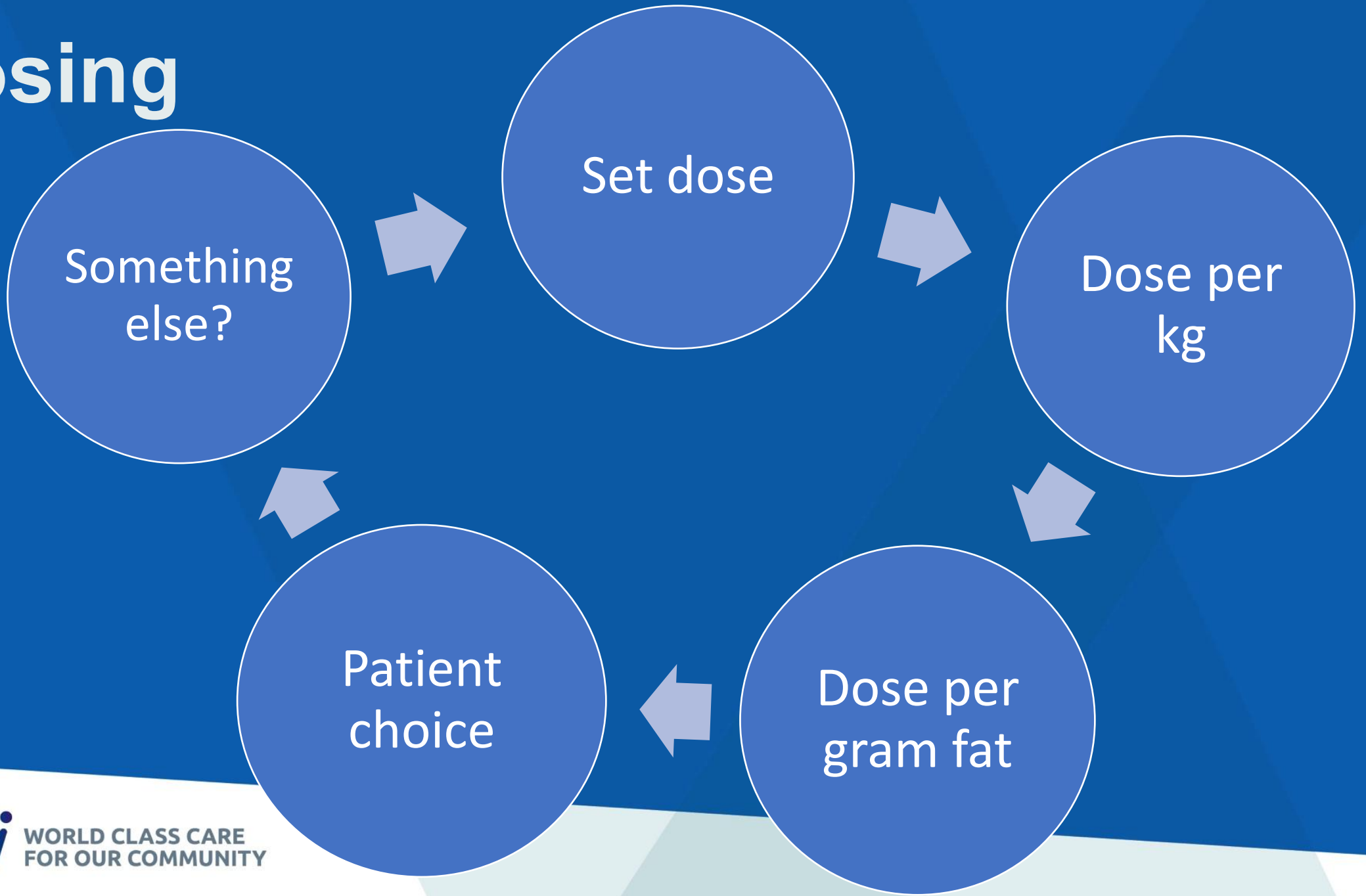
Dosing



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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).

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

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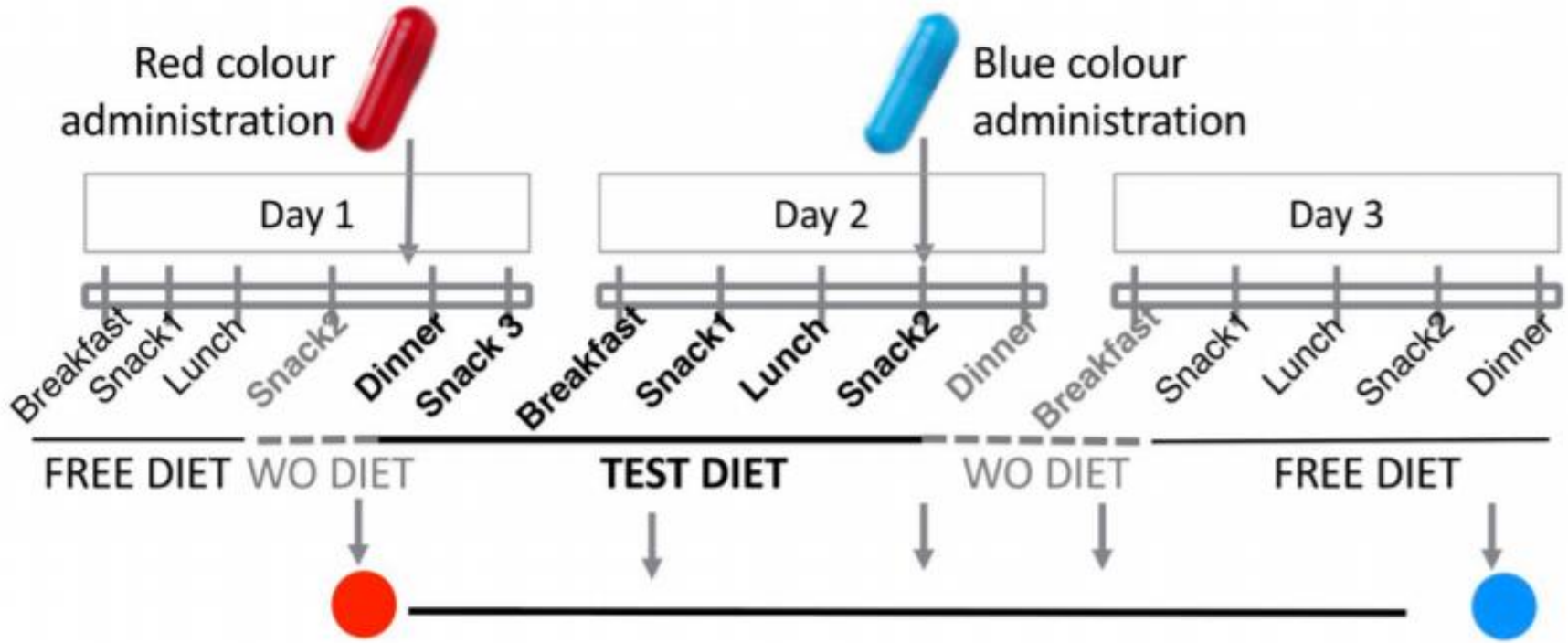

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$$IOD = \frac{g(90\%_{clinical\ target\ CFA}) - \beta_0 - (\beta_1 \cdot transit\ time) - (\beta_3 \cdot age) - (\beta_4 \cdot PPI\ intake)}{\beta_2}$$

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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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.)

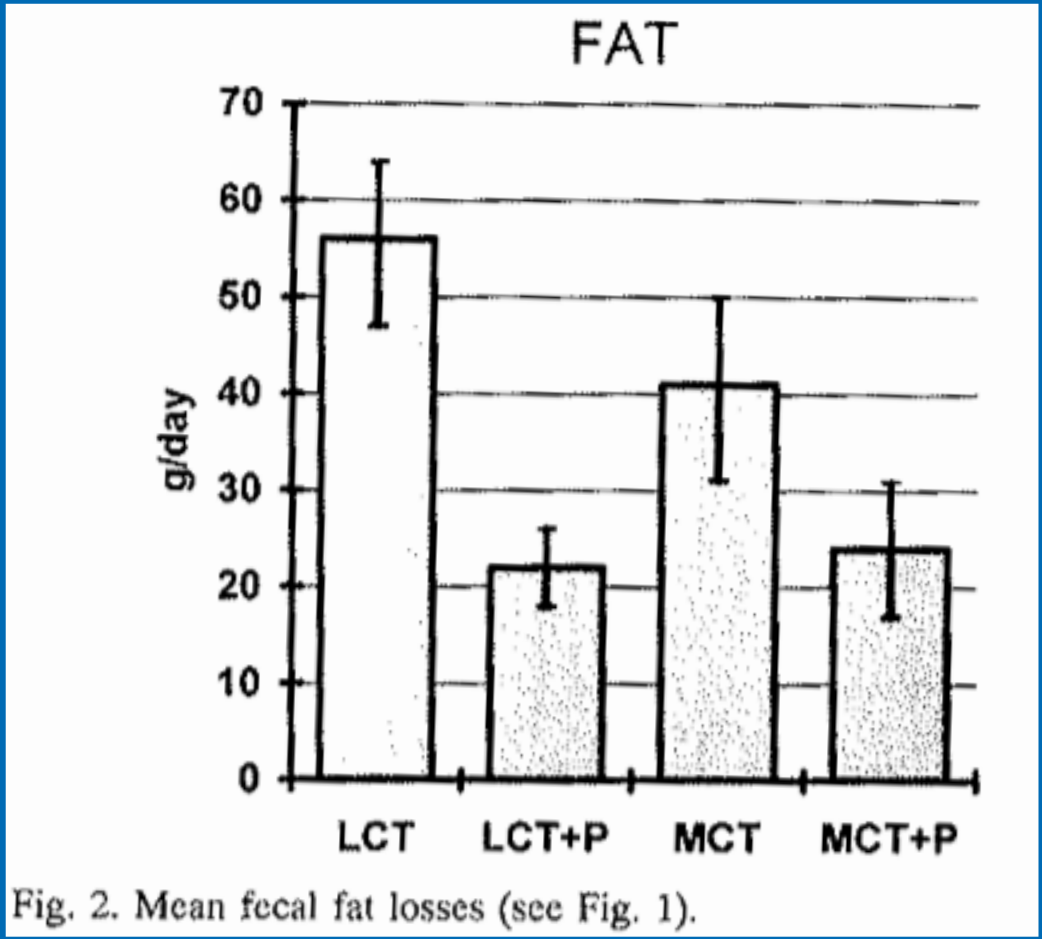

Fig. 2. Mean fecal fat losses (see Fig. 1).

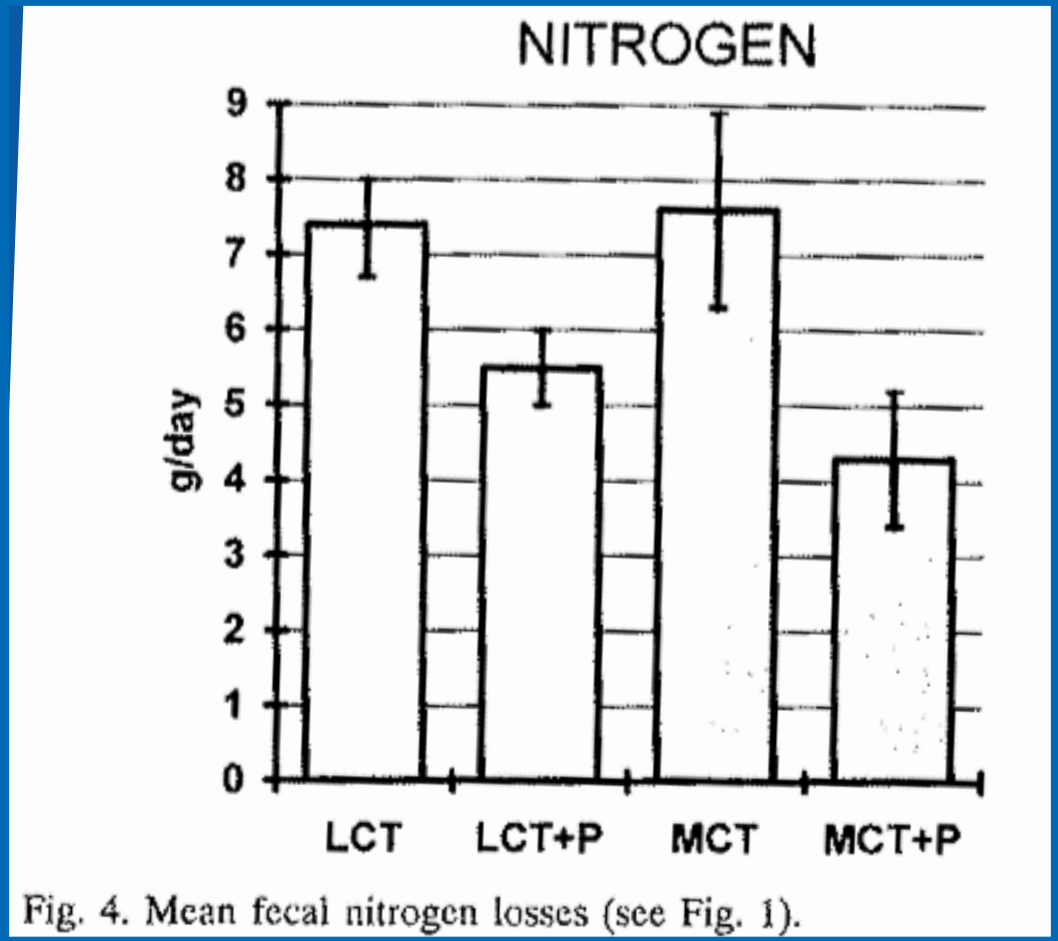

Fig. 4. Mean fecal nitrogen losses (see Fig. 1).

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

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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

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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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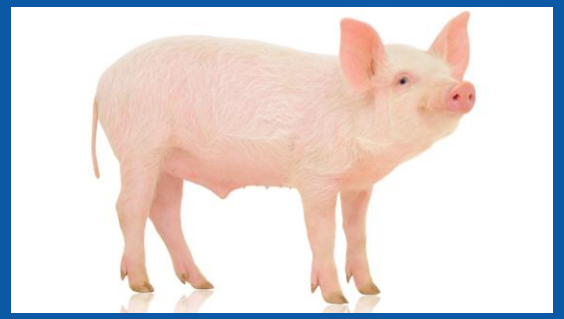
Recommendations for clinical practice

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 symptom control
- Snacks *vs*. meals
- Nutritional supplements

Prevent denaturation

- <25ºC
- ?Proton pump inhibitor?
- Avoid swallowing with hot food/fluids

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BMJ Open Gastroenterology

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

Mary E Phillips [1], Andrew D Hopper,[2] John S Leeds [3], Keith J Roberts [4], Laura McGeeney,[5] Sinead N Duggan,[6] Rajesh Kumar[7]

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

- Exocrine insufficiency is progressive, and doses escalate with time
- A few 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

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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
- Other conditions can mimic PEI
- More data needed to explore relationship with survival in pancreatic cancer.

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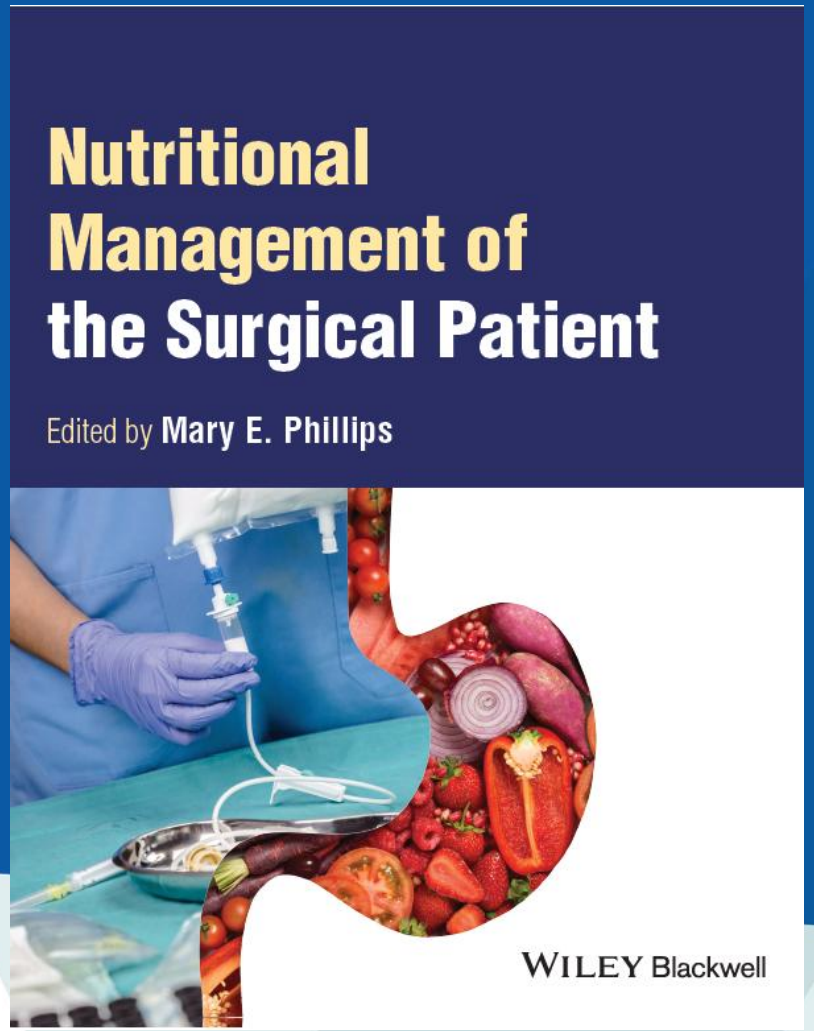
More information on managing pancreatic (and other) surgical patients



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The PERT shortage….

UK shortage of critical drug forcing pancreatic cancer patients to skip meals

One pharmacist described scarcity of life-saving Creon as 'worst stock shortage' they have dealt with

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National Patient Safety Alert

Department of Health & Social Care

NHS England

Shortage of Pancreatic enzyme replacement therapy (PERT)

Position Statement: Pancreatic enzyme replacement therapy (PERT) shortage – advice for the management of adults with pancreatic exocrine insufficiency

Phillips M.E[1,3], McGeeney L.M[1], Watson K-L[2], Lowdon J[2].

Phase 1: What to do when you have a supply

- Do not stockpile
- Check expiry dates
- Put next prescription request in as soon as the last one is issued, and check it has been authorised
- Ensure your PERT is optimised – spread out the dose, store <25°C Speak to your GP about accessing imported medications so everyone is aware in case you have less than 2 weeks left

(HCP's – please add it to every letter)

iNForm your GP

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Advice to GP's & Community Pharmacists

- Prescribe one month's worth at a time
- Authorise multiple prescriptions
- Prepare – be aware of imported procedures and set up necessary accounts with wholesalers and Pharmacies managing central stocks

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Phase 2: What to do if you think you need to increase your dose

- If you have CF – speak to your specialist centre
- Before increasing your PERT:
  - Add a PPI if not on one already
  - Space out throughout meals
  - Store below 25^{o}C
- Consider peptide ONS in place of polymeric to reduce need for PERT
- Speak to your Dietitian / Doctor / Nurse Specialist if you are struggling with symptoms or your weight.

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PERT prescription management

- Reassure patients
- Ensure optimal use of existing product: timing, storage
- Prioritise Creon 10,000 for children and those unable to swallow larger capsules
- Prioritise Nutrizym 22 for those unable to tolerate Creon
- Consider PPI if not on one already
- If nutritionally well, consider using loperamide to optimise bowel symptoms rather than a dose escalation
- If gastrically fed, consider giving PERT via PEG/NG at mealtimes in those eating alongside feed.
- Consider peptide ONS in place of polymeric to reduce need for PERT

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Other considerations

- Blood glucose control – higher risk of hypo's and poor correction of hypo's.
- Vitamin K – patients on anti-coagulation should be flagged to their GP as may need more regular monitoring
- Medication absorption – seizure medication, oral contraceptive pills. Consider a secondary form of contraception at this time.
- Consider falls – faecal urgency in vulnerable patients

Phase 4: What to do if you have <2 weeks supply left

- Don’t panic!
- Check with manufacturer helpline to source stock:: **Creon: 0800 8086410; Nutrizym 0800 0902408**
- Speak to your Pharmacist AND GP to arrange a prescription for an import – in most ICBs this is PANGROL.
- If you have completely run out – make a same day emergency appointment with your GP
- If you are under the care of a local hospital, contact your team there to request an emergency rescue prescription.

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UK medications are licenced

- Prescriber takes on all the risk
- Be aware of local formulary restrictions
- Need MHRA approval
- 1-4 weeks lead time

Status	Description
Preferred	Product has been agreed as the preferred choice for initiation and continuation in Primary, Secondary or Tertiary care settings.
GREEN	Product has been agreed as appropriate for initiation and continuation in Primary, Secondary or Tertiary care settings.
Amber *	Now referred to as "Blue" but some Amber Star drugs remain pending review. Prescribing initiated and stabliised by specialist but has potential to transfer to primary care WITHOUT a formal shared care agreement. Please note that in some circumstances a specialist may recommend that prescribing can be started in primary care.
BLUE	Prescribing initiated and stabilised by specialist but has potential to transfer to primary care WITHOUT a formal shared care agreement. Please note that in some circumstances a specialist may recommend that prescribing can be started in primary care.
AMBER	Prescribing initiated and stabilised by specialist but has potential to transfer to primary care under a formal shared care agreement
RED	Product is for specialist use in secondary / tertiary care. Prescribing to be initiated and continued by the specialist clinician.
BLACK	Not to be routinely commissioned (prescribed) in any care setting (primary or secondary care). This may be due to a lack of good clinical evidence, cost effectiveness, concerns over safety or due to the availability of more suitable alternatives. These are drugs that have been reviewed by the Prescribing Clinical Network and are not recommended for use in any healthcare setting across Surrey & North West facing Sussex health economy. As such, drugs classified as Black should be considered as non-formulary.
	Initiation of this drug is NOT recommended in any health care setting across Surrey & North West facing Sussex CCGs. Prescribers can, however, continue to prescribe for patients already taking this drug
OTC	Patients should be advised to purchase if appropriate.

What can specialist centres do?

- Support
- Rescue prescriptions where needed?
- Liaise with local medicines management teams
- Work with pharmacy team to make DTC applications for imported medications if needed
- Consider putting this on your Trust risk register
- Out of office with information on them

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