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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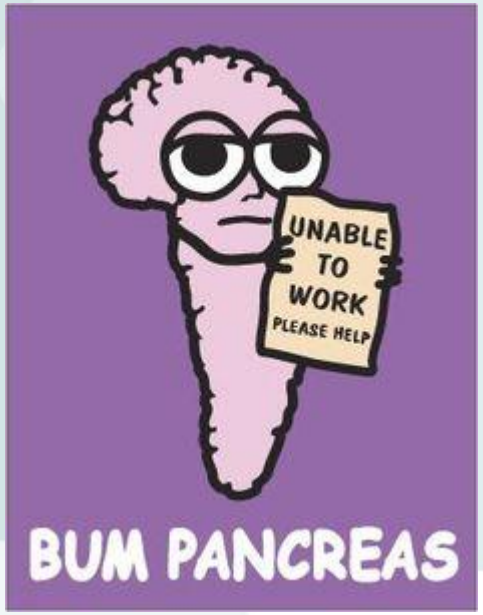


Introduction

Anatomy and function of the pancreas

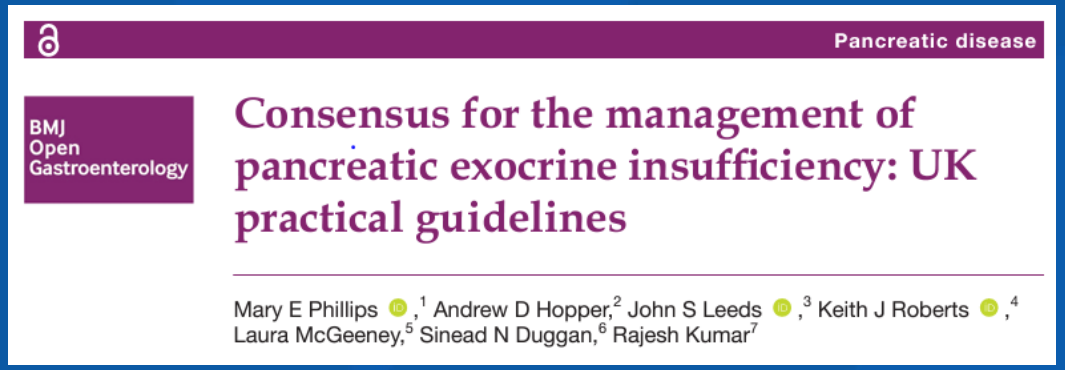
Causes and incidence of pancreatic exocrine insufficiency

Impact of pancreatic exocrine insufficiency

Managing pancreatic enzyme replacement therapy

Recommendations for practice

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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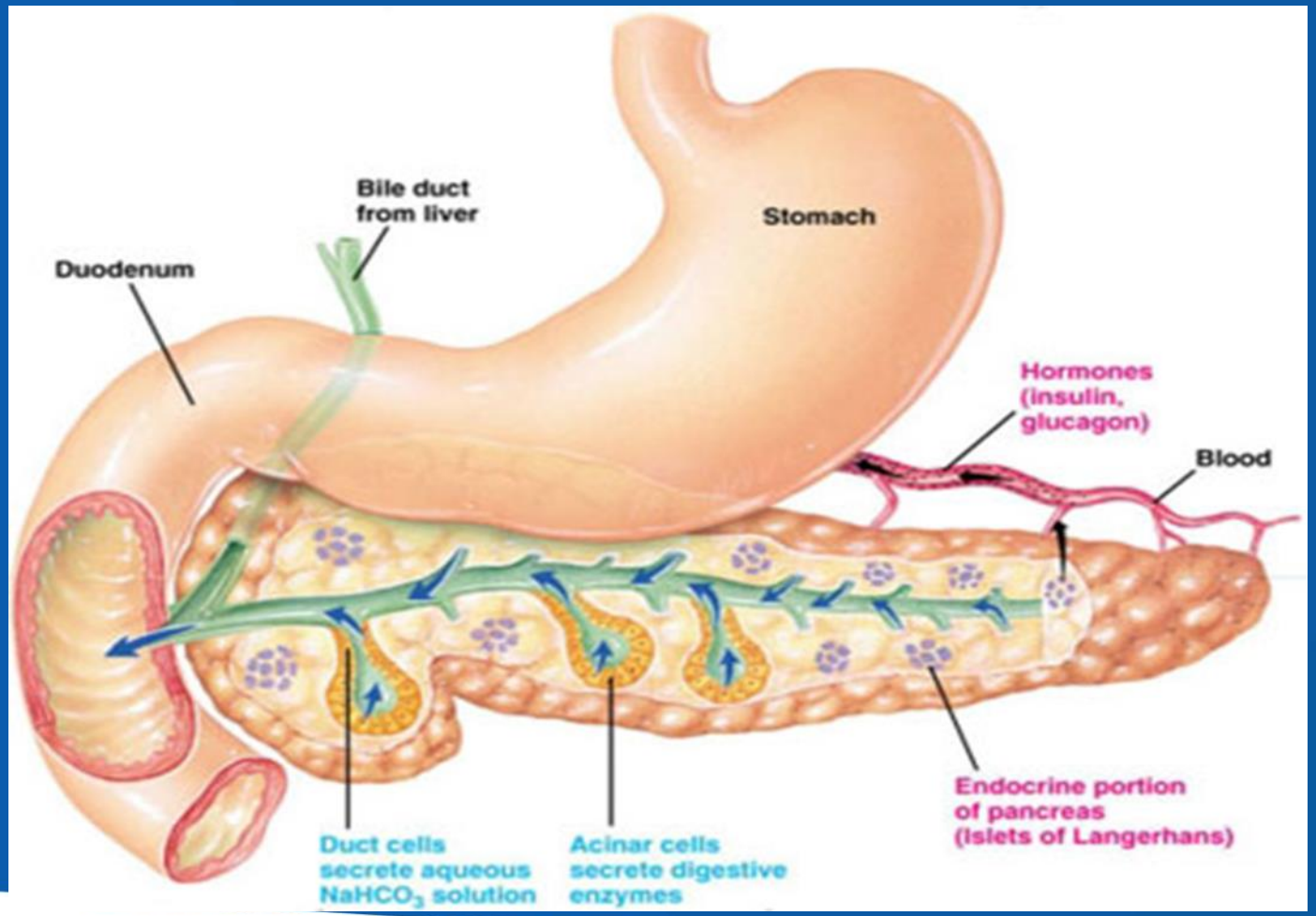
Anatomy and function



- 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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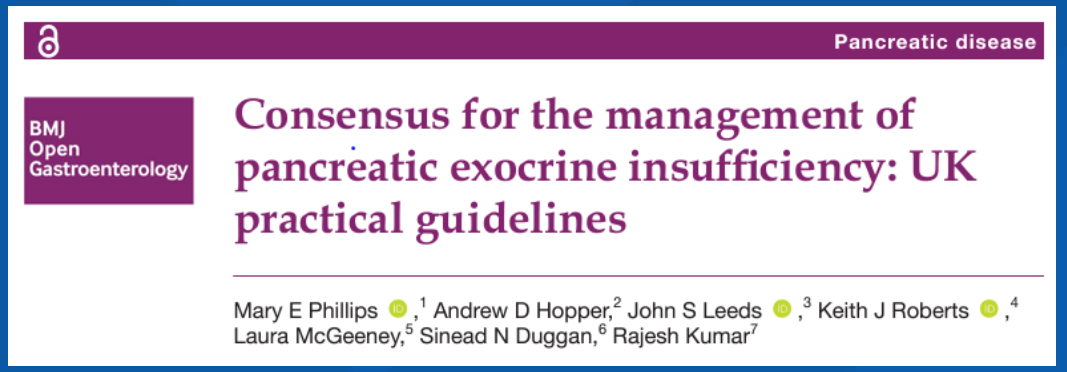

Definition and diagnosis of PEI

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

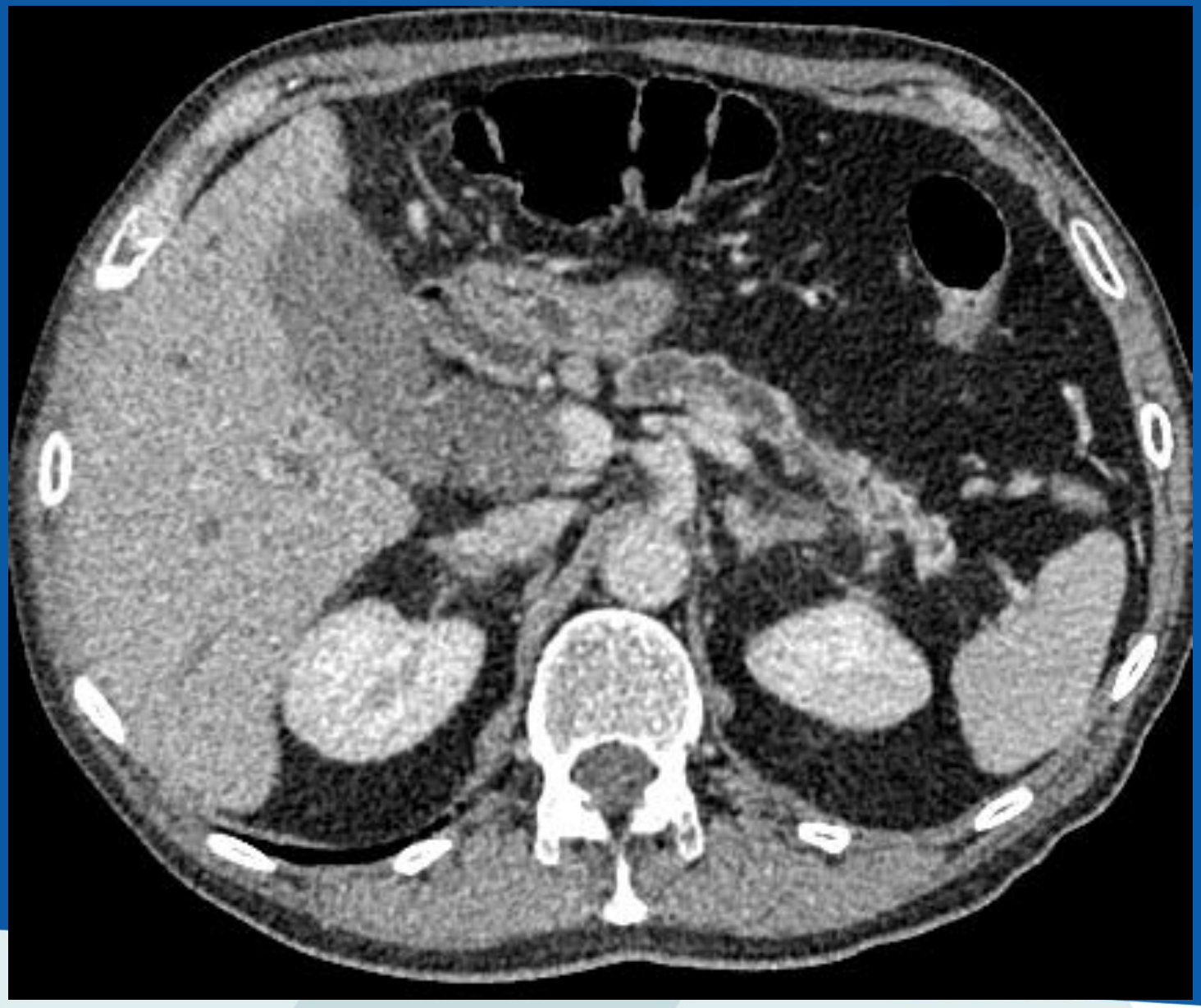
Pancreatic Function Tests

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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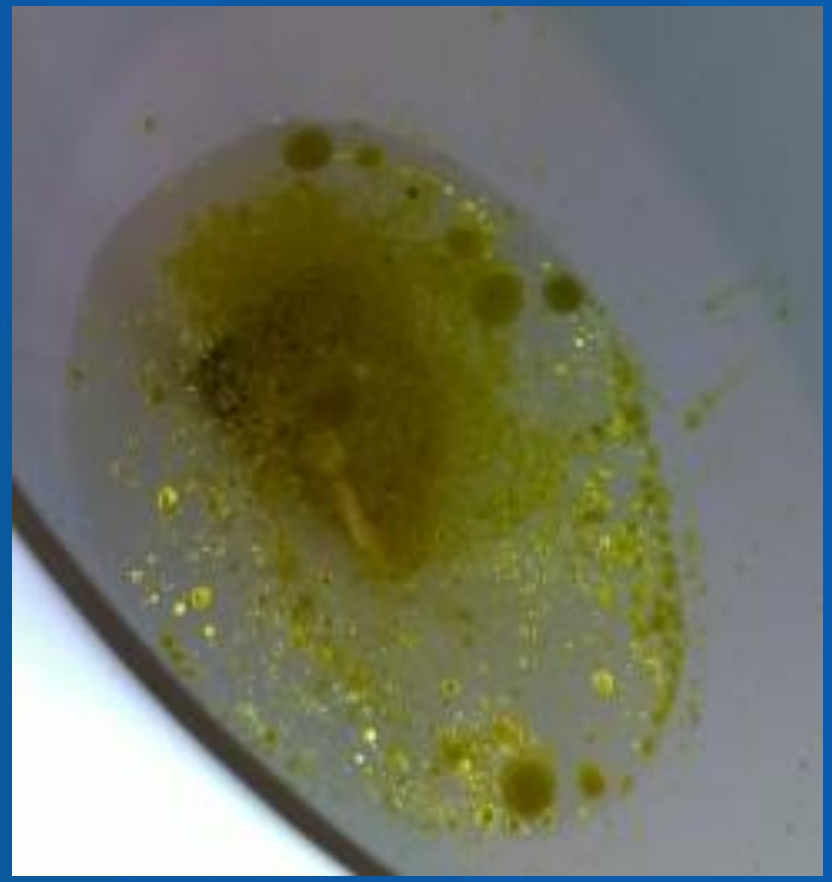
Clinical symptoms (1)

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

Trial design

Retrospective observational study

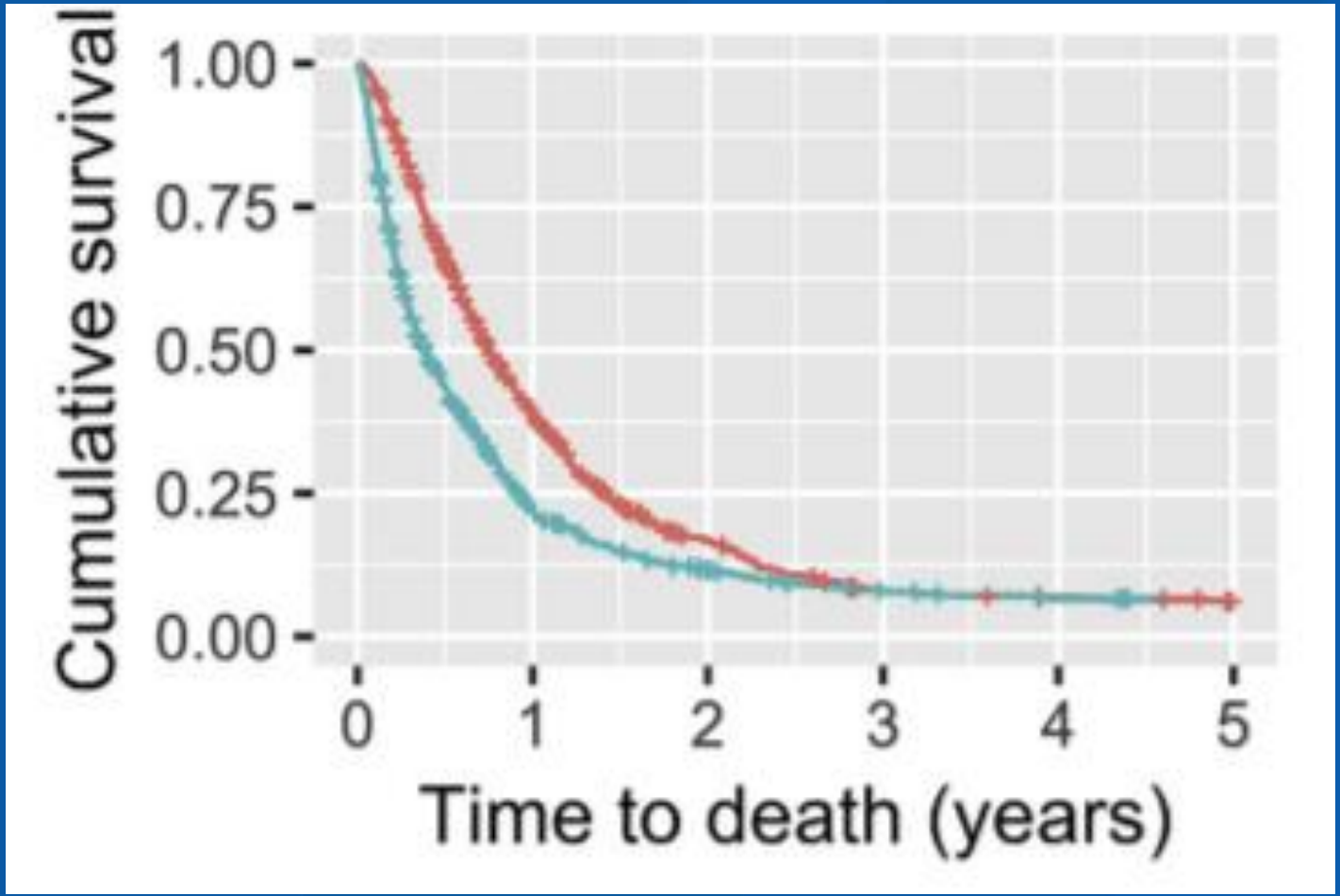
PDAC 1998 – 2015

Excluded those with concurrent pancreatitis, PERT prior to diagnosis

All patients

PERT

Non PERT



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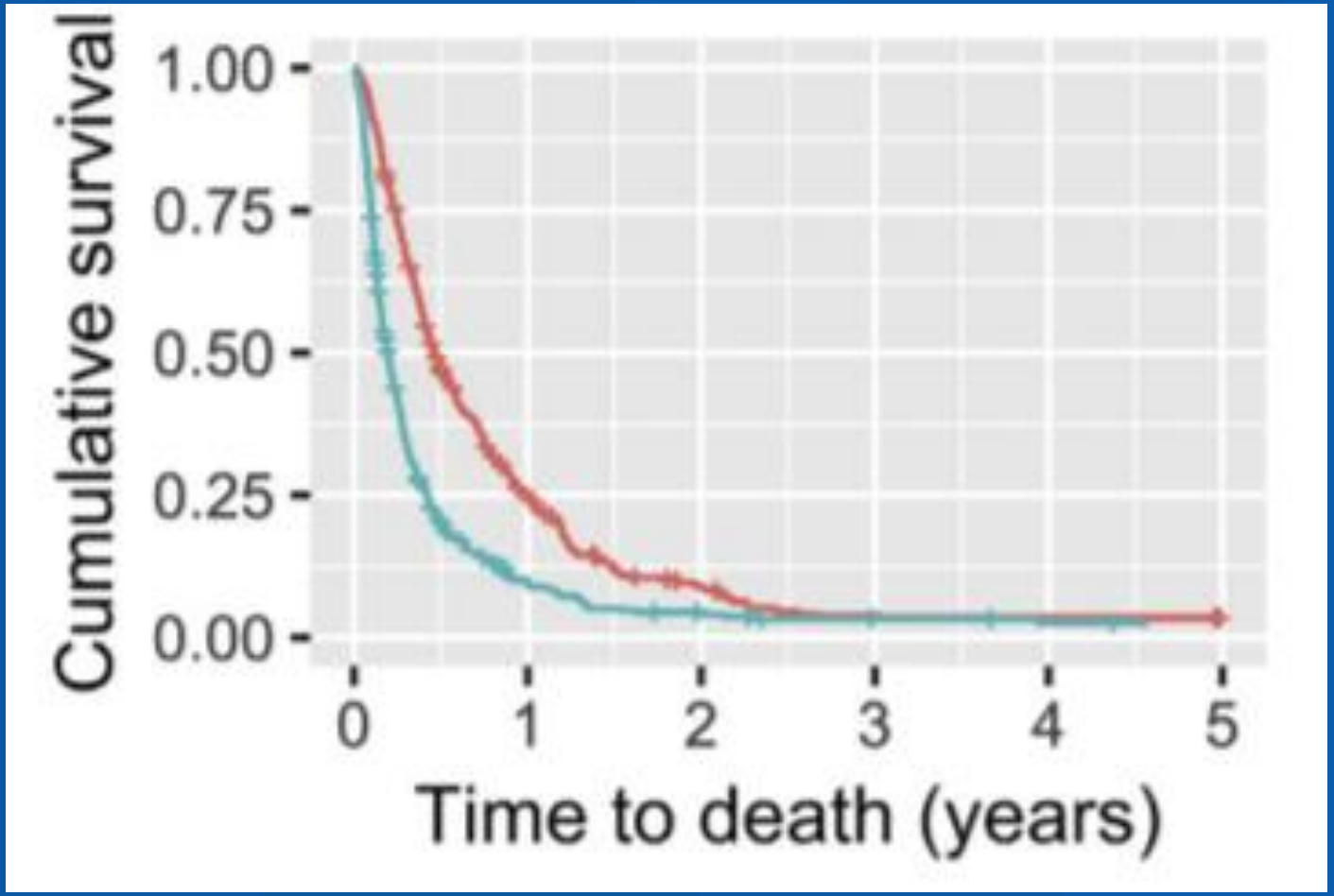
No surgery, no chemo

PERT

Non PERT



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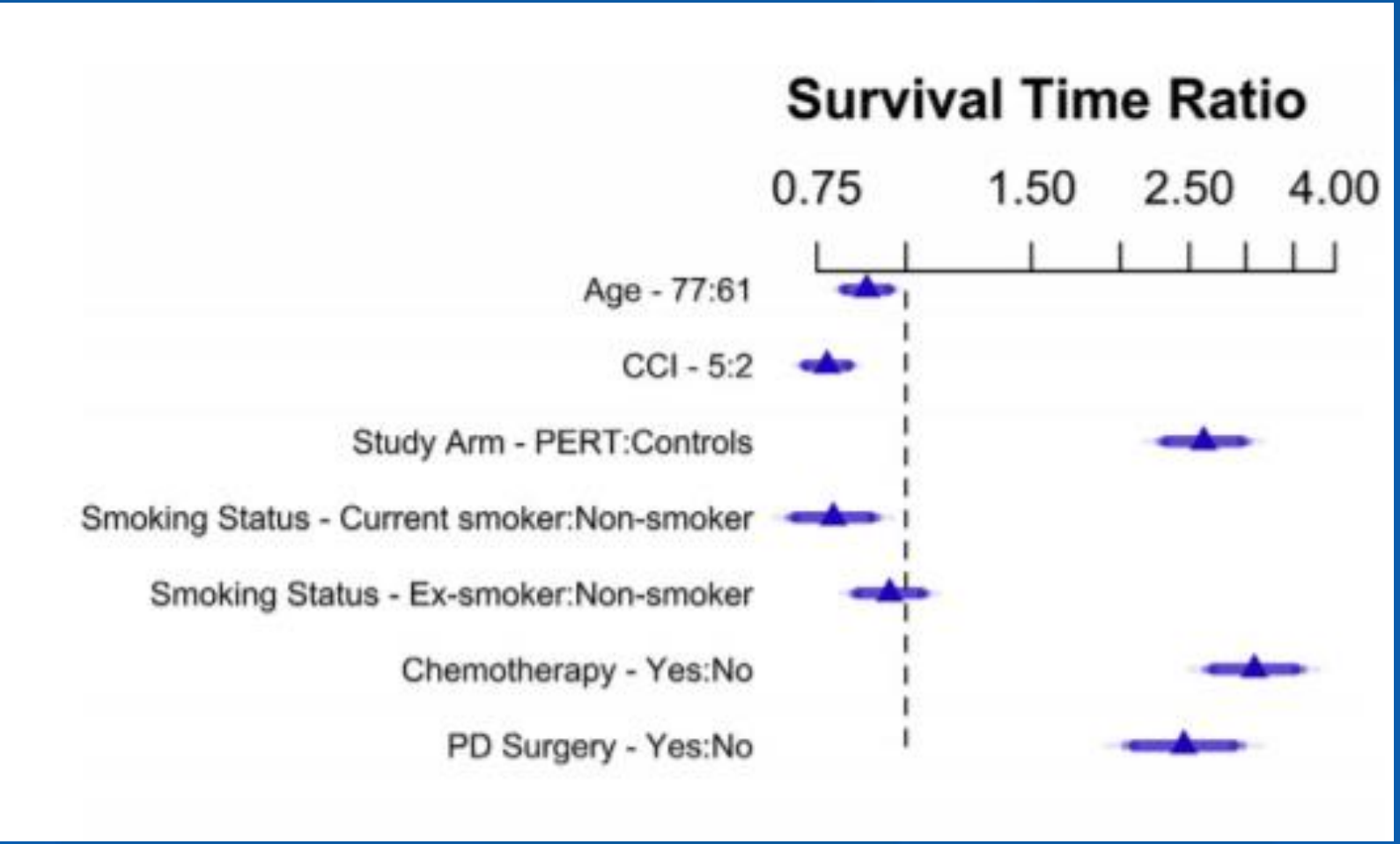
Factors influencing survival



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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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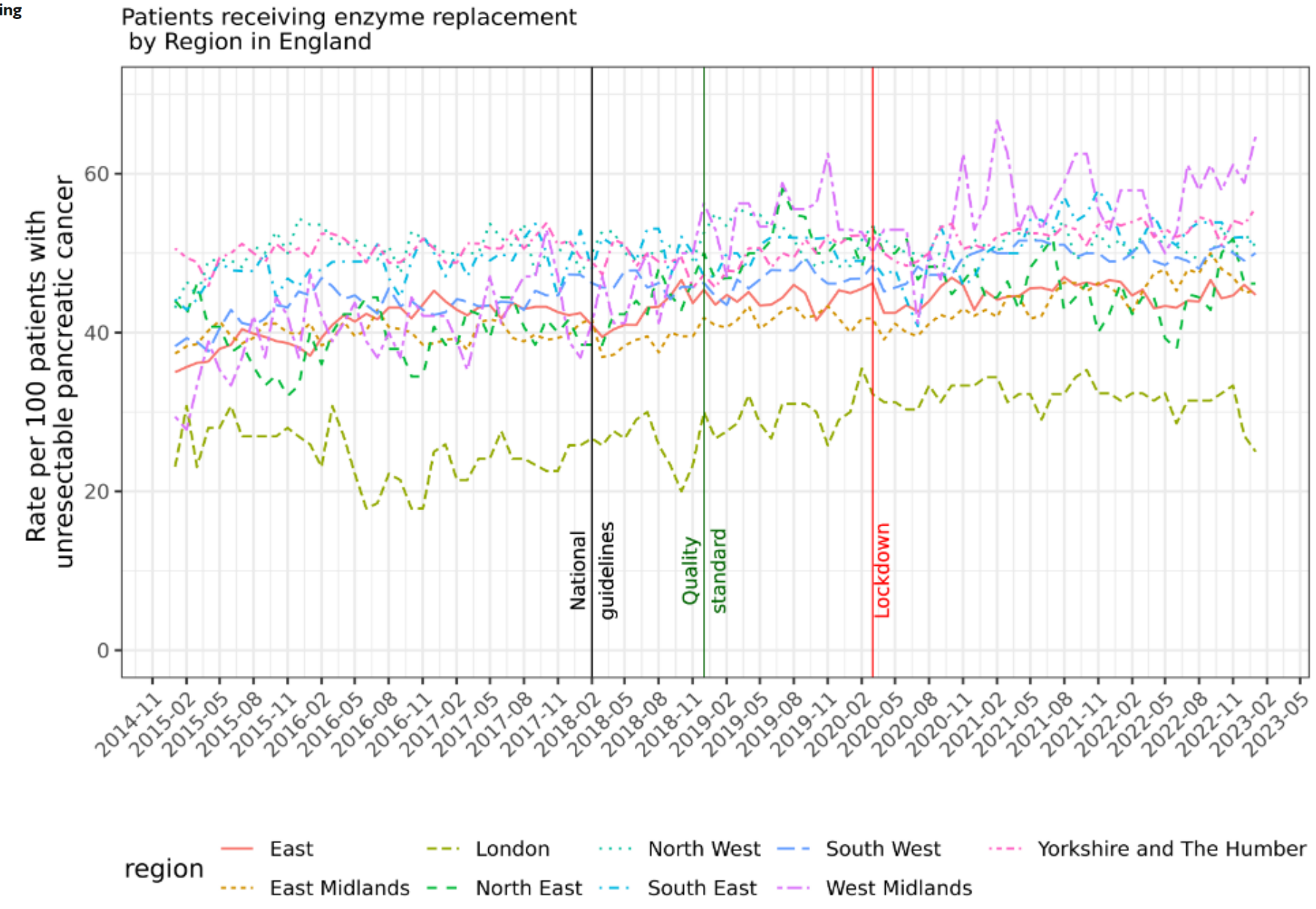
Ricochet study (2021)

- 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

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,*]

Pancreatology 15 (2015) 19–24

Contents lists available at ScienceDirect

Pancreatology

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

Review article

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,*]

Ann Surg Oncol (2018) 25:308–317
https://doi.org/10.1245/s10434-017-6216-5

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – PANCREATIC TUMORS

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]

Published in final edited form as:
J Gastrointest Surg. 2012 August ; 16(8): 1478–1486. doi:10.1007/s11605-012-1923-5.

Impact of Sarcopenia on Outcomes Following Resection of Pancreatic Adenocarcinoma

ANTICANCER RESEARCH *38*: 1061-1066 (2018)
doi:10.21873/anticanres.12323

Visceral Adipose Tissue and Skeletal Muscle Index Distribution Predicts Severe Pancreatic 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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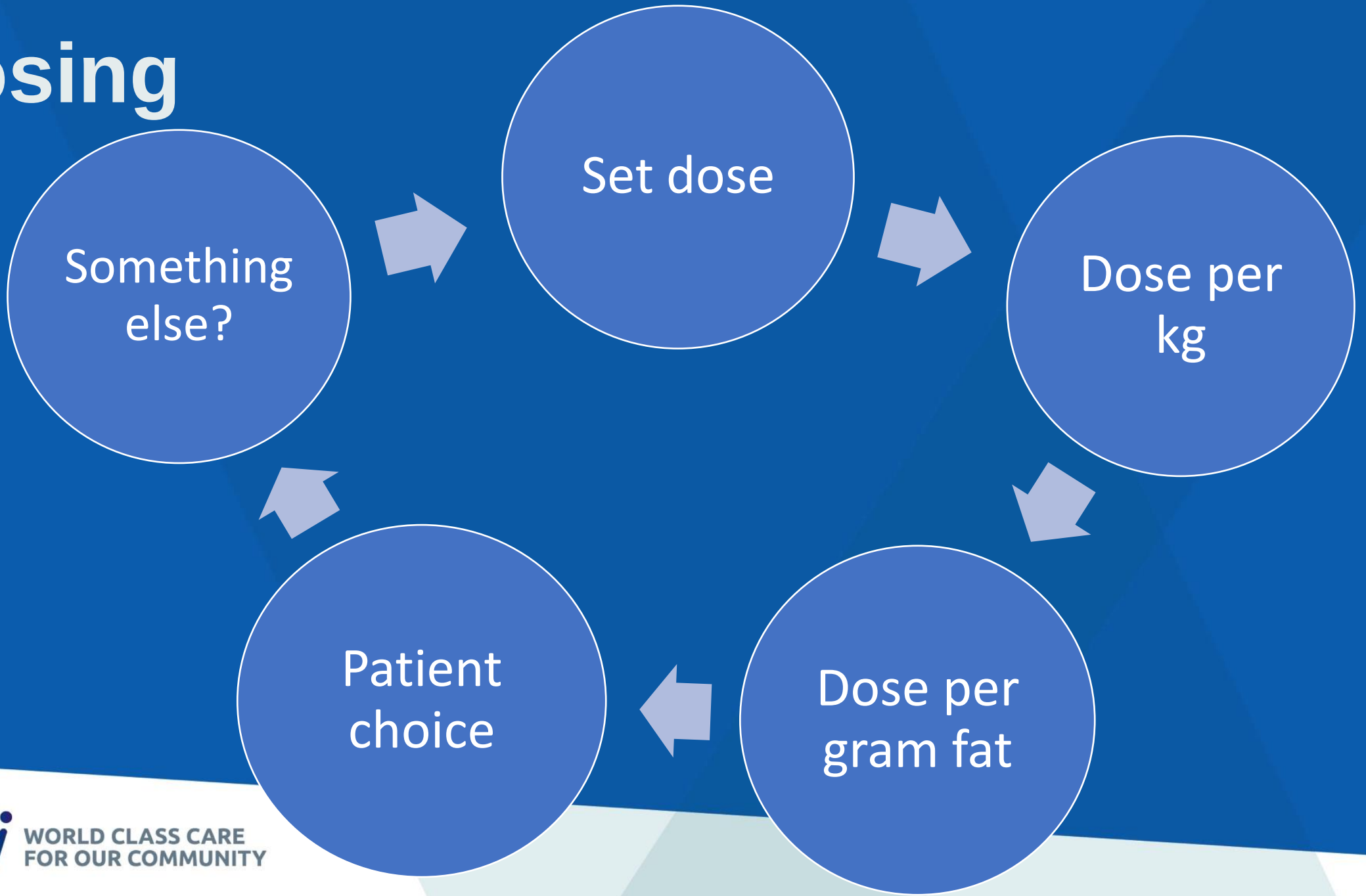
Dosing



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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).

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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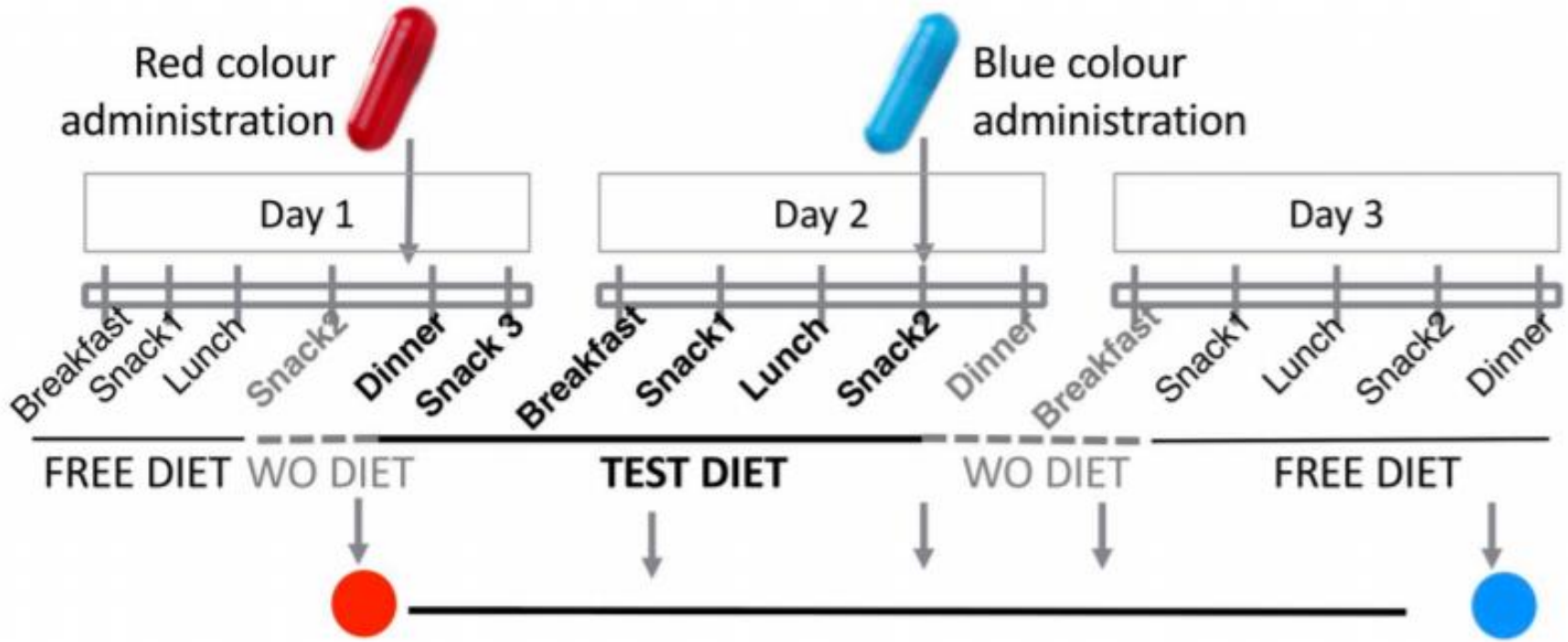

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$$IOD = \frac{g(90\%_{clinical\ target\ CFA}) - \beta_0 - (\beta_1 \cdot transit\ time) - (\beta_3 \cdot age) - (\beta_4 \cdot PPI\ intake)}{\beta_2}$$

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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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.)

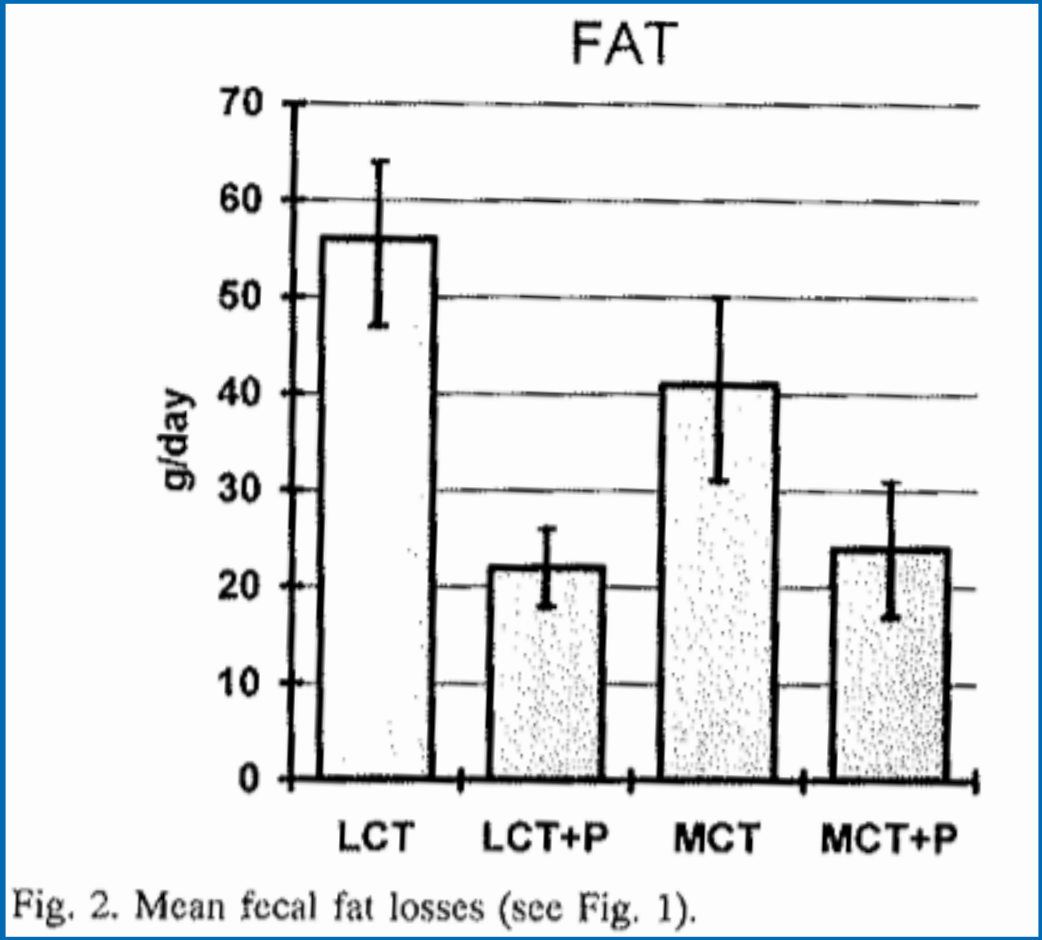

Fig. 2. Mean fecal fat losses (see Fig. 1).

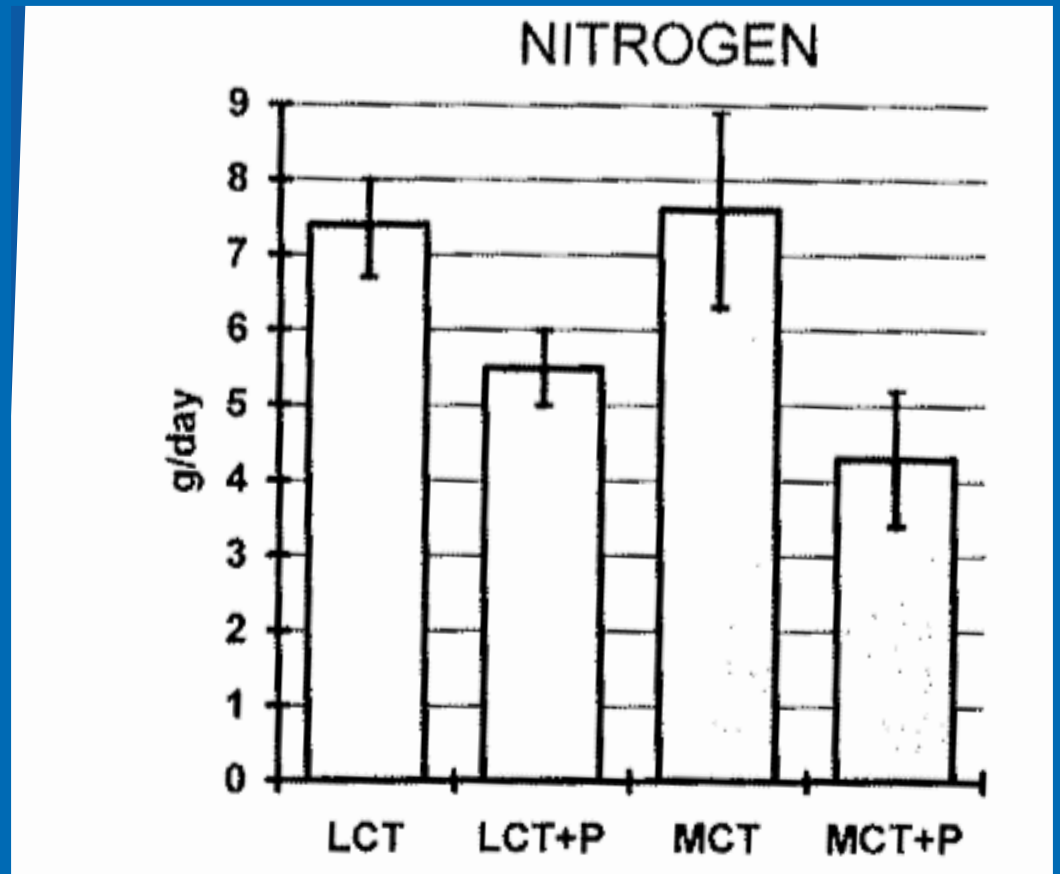

Fig. 4. Mean fecal nitrogen losses (see Fig. 1).

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

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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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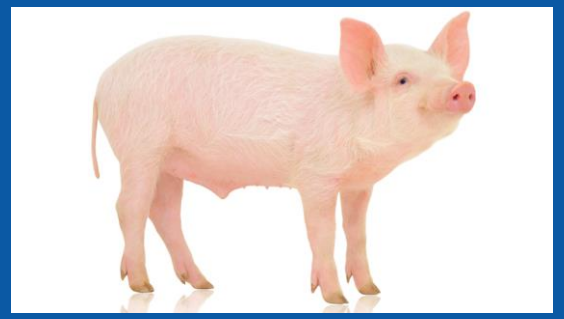
Recommendations for clinical practice

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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Case 1

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- 78 year old female
- Metastatic pancreatic cancer – liver mets
- Declined palliative chemotherapy
- Bowels open once a day: type 1 (pellet type stool)
- Large volume hard stool
- Crampy abdominal pain
- 5% weight loss each month despite eating well
- Functionally well – caring for Grandchildren

- Taking high dose opioids for pain relief
- Commence laxatives
- Once bowel symptoms improved – then start PERT
- Biggest symptom was constipation

Case 2

- 69-year-old female
- Localised pancreatic ductal adenocarcinoma
- Distal pancreatectomy and splenectomy – 1cm lesion removed from tail of pancreas
- Bowels open 4 x a day loose and watery
- Gaining weight, 1-2kg per month
- Eating well

- Investigate:
  - Total specimen 2cm tail of pancreas
  - Head and body of pancreas enhances normally, no duct dilatation
  - Faecal elastase >500ug/g
  - Vitamin and mineral levels normal

Outcome

- No nutritional compromise
- PEI = **Failure of the pancreas to secrete enough enzymes to achieve normal digestion**

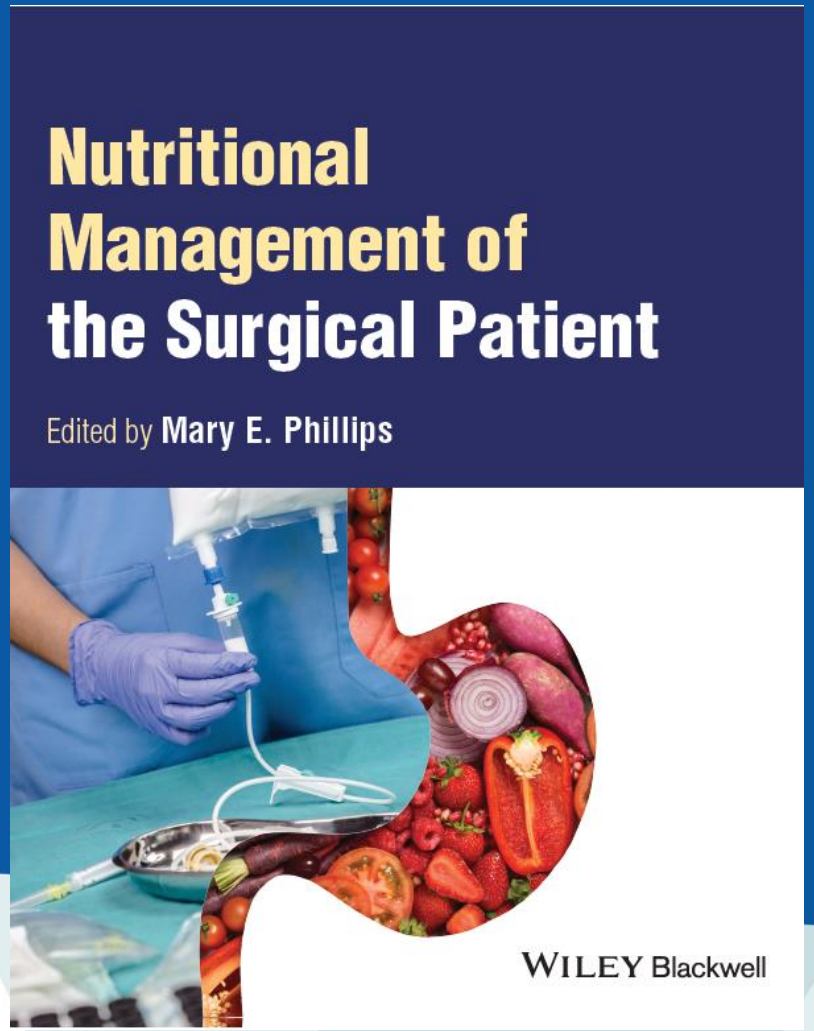
PDAC is a Red Herring

- Further investigations – diagnosed small intestinal bacterial overgrowth
- Symptoms resolved with antibiotics.

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.

More information on managing pancreatic (and other) surgical patients



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