Managing pancreatic exocrine insufficiency

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Honoria received from Viatris and Nutricia Clinical Care, Di

Introduction: setting the scene

- Definition of PEI
- Anatomy and physiology of the pancreas
- Causes of PEI
- Benefits of PERT
- Dosing PERT
- Recommendations for clinical practice

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Take home messages

- 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.

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Definition

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

"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)

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

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

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Introduction

- Anatomy and function of the pancreas
- Causes and impact of pancreatic exocrine insufficiency
- Benefits of pancreatic enzyme replacement therapy
- Dosing
- Recommendations for practice

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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)

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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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Anatomy and function of the pancreas

Causes and incidence of pancreatic exocrine insufficiency

Benefits of pancreatic enzyme replacement therapy

Dosing

Recommendations for practice

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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

Layer et al, 2001

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Incidence of PEI after surgery

12% following central pancreatectomy
20% following distal pancreatectomy
20-45% pre-op for head of pancreas tumours
70-98% following pancreatico-duodenectomy

(Phillips M, Pancreatology 2015;15(5) 449-55)

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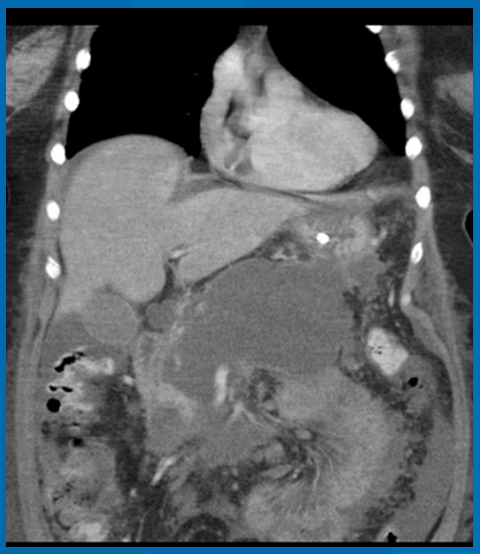
Incidence of PEI after acute pancreatitis

- 60% of patients with SAP develop PEI
- Long term follow up ¼ of all patients with AP have PEI
- Potential quality of life benefits
- Severe malnutrition
- Multiple confounding factors

(Xu et al, 2012, Kahl et al, 2014)



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Incidence of PEI in chronic pancreatitis

Several studies have examined the incidence of PEI in those with chronic pancreatitis. Chronic pancreatitis is a progressive disease.

- At diagnosis: 8–22%
- 13-26 years: 44–48%
- 14-36 years: 91–100%

Mullhaupt et al, 2005; Layer at al, 1994; Waljee et al, 2009

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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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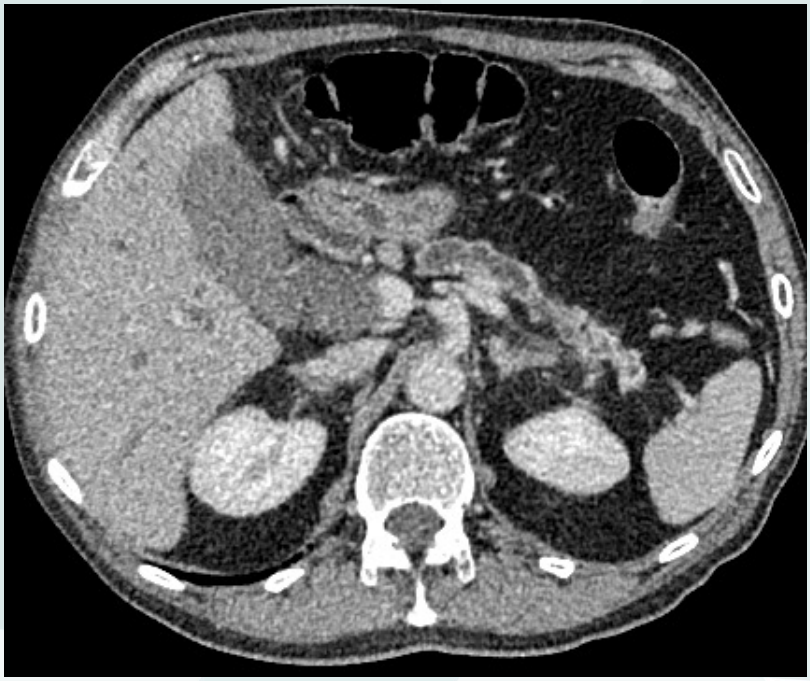

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Clinical symptoms (1)

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

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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)

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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);

Large retrospective studies show link with survival in all cases (Roberts et al, 2019)

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….

QOL

"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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RICOCHET

Pancreatology xxx (xxxx) xxx

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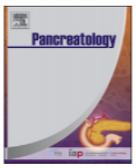

Pancreatic enzyme replacement therapy in patients with pancreatic cancer: A national prospective study

The RICOCHET Study Group on behalf of the West Midlands Research Collaborative[1, 2]

West Midlands Research Collaborative, Open Plan East, Second Floor, Institute for Translational Medicine, University of Birmingham, Edgbaston, Birmingham, B15 2TH, UK

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Introduction: RICOCHET

- National prospective audit (ReceIpt of Curative resection Or palliative Care for HEpatopancreaticobiliary Tumours)
- Trainee led
- All patients presenting with pancreatic cancer / malignant biliary obstruction in a 16 week period with 90 day follow up
- Patients who died within 14 days of their first MDT were excluded
- 84 hospitals took part (25 tertiary centres; 59 non-HPB surgical hospitals)
- N = 1350

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Results

- 429 patients potentially resectable
- 921 patients unresectable
- Identified a wide variation across centres

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Results

- PERT was prescribed in
  - 54.5% of all patients
  - 74.5% of potentially resectable patients
  - 96.9% of resected patients
  - 63.7% of patients having neo-adjuvant

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Results

Factors impacting prescription

- Seen by a dietitian (76.7% vs 19.9%, p<0.001)
- Seen in a tertiary centre (55.2-84.6% vs 42.3% p<0.001)
- Seen by a CNS (64.8% vs 35.2%, p<0.001)
- Performance status (0 – 61%, 1 - 56.4%, 2 – 51.3%, >2 - 34.5% p<0.001)
- Respectability (74.4% vs 45.3%, p<0.001)
- Nutritional Supplements prescribed (78% vs. 25.3% p<0.001)
- Gender Male (58.2% vs Female. 50.6% p=0.005)
- Age – younger patients more likely to received PERT (<63 years old 62.9% vs. > 81 years old 36.9% p<0.001)

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Benign disease

- Reduces non-alcoholic fatty liver disease (Petzel & Hoffman, 2017)
- Survival benefit in those having surgery for CP
  (Winny et al, 2013, Iglesia-Garcia et al, 2018)
- ? Prevention of long term vitamin and mineral deficiencies
  (Yu et al, 2011, Livingstone et al, 2003, Armstrong et al, 2007.)
- Higher prevalence of osteopathy (Duggan et al, 2014)
- QOL in acute pancreatitis (Kahl et al, 2014)
- Higher incidence of Cardiovascular incidents (Iglesia et al, 2018)

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Pancreatic surgery

- 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)
- Sarcopenia is associated with higher complication rates (Sandini et al, 2016, Yamane et al, 2018)
- Sarcopenic Obesity is associated with failure to rescue (Pecorelli et al, 2018)

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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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Dose

- 10,000 un[illegible] lipase TDS

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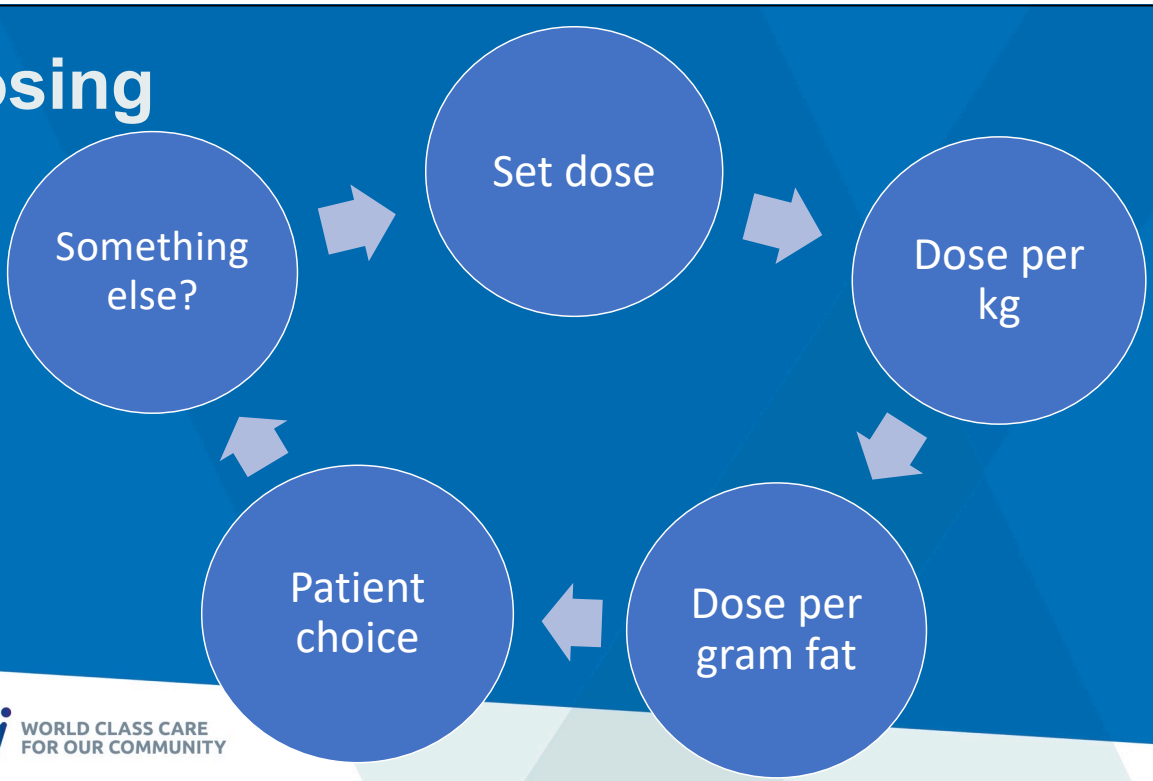
Dosing



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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 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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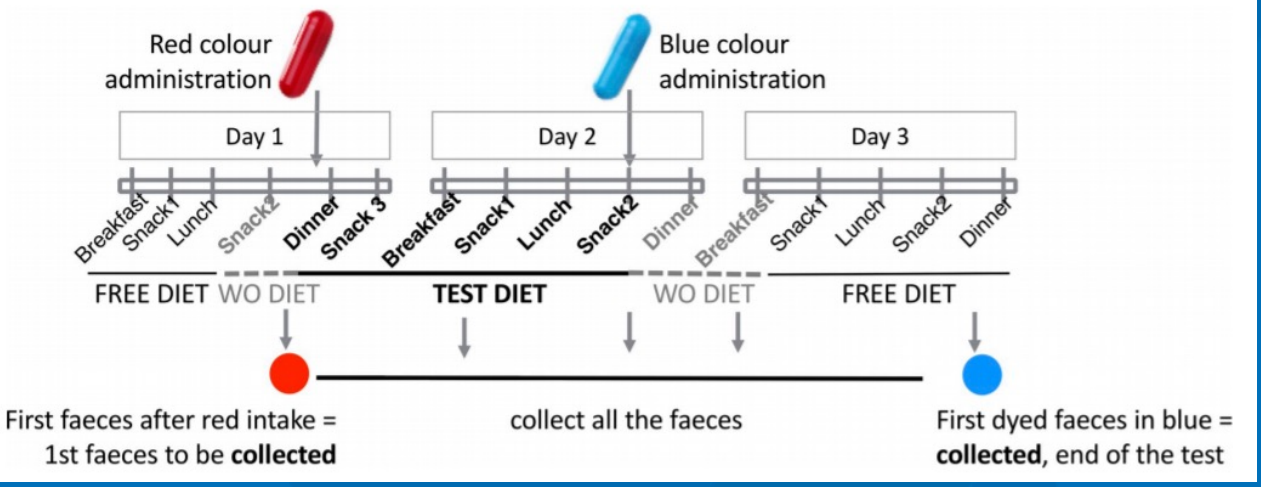

PLOS ONE | https://doi.org/10.1371/journal.pone.0213216 March 12, 2019

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

- 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?

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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%)
- Reduction in nitrogen losses in stool with PERT

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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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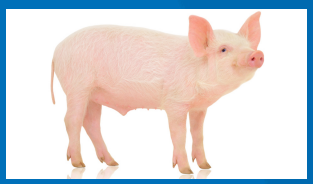
Recommendations for clinical practice

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°C
- ?Proton pump inhibitor?
- Avoid swallowing with hot food/fluids

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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

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What do you need to know :PEI

- 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

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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
- More data needed to explore relationship with survival in pancreatic cancer.

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