G.14 Exocrine pancreatic insufficiency

Review question: In people with cystic fibrosis, what is the effectiveness of enzyme replacement therapy in the treatment of exocrine pancreatic insufficiency?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Mitchell, E. A., Quested, C., Marks, R. E., Pinnock, R. E., Elliott, R. B., Comparative trial of viokase, pancreatin and Pancrease pancrelipase (enteric coated beads) in the treatment of malabsorption in cystic fibrosis, Australian Paediatric Journal, 18, 114-7, 1982 Ref Id 346478	Sample size n=12 Characteristics Group: children Age (mean±SD): 9.6±2.1 Gender (M/F): 4/ 8 Inclusion criteria Patients with CF (diagnosis established by abnormally high sweat and sodium and chloride levels and increased faecal fat excretion). Chest disease fairly stable. Antibiotics given when medically indicated.	Interventions Intervention 1: Non-EC low-dose (Viokase® 16 capsules)* Intervention 2: Non-EC high-dose (Viokase® 32 capsules)* Intervention 3: EC low-dose (Pancrease® 11 capsules)	Details Procedure: carried out in 4 sequential 4-week periods. A 3-day stool collection was taken out at the end of each 4-week treatment period. No attempt was made to modify the diet. Outcome measure: Dietary fat intake was estimated from a 3-day food record kept by the parents during each of the stool collection periods, and stool fat measure by previously described methods (Van	Results Faecal fat (g/kg/day) 3.2±0.8 vs. 3.2±0.9 Faecal fat (g/day) 8.7±4.1 vs. 11.5±6.9 Fat absorption (%) 89.5±4.2 vs. 85.4±11.2 Stool frequency (bowel actions/ day) 1.7±0.7 vs. 1.8±0.8 Abdominal pain	Limitations Assessed with Cochrane risk of bias tool: Random sequence generation (selection bias): Unclear risk of bias (Not reported) Allocation concealment (selection bias): Unclear risk of bias (Not reported) Blinding (performance bias and detection bias): Unclear risk of bias (Not reported)

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Country/ies where the study was carried out New Zealand Study type Cross-over trial Aim of the study To examine the effectiveness of Pancrease® with that of a widely prescribed conventional product (Viokase® pancreatin capsules) COMPARISON 2. HIGH DOSE VS LOW DOSE Study dates Not reported. Source of funding Not reported, but Pancrease® pancrealipase capsules were supplied by Ethnor Pty. Ltd.	Exclusion criteria Not reported.	Pancreatin or pancrealipase: pancrealipase Product name: Pancrease® Constituent enzymes: each capsule contains 4,000 USNF lipase units; 25,000 USNF protease units; 20,000 USNF amylase units Type of PERT: EC Formulation: beads Timing of administration: not reported Number of tablets and doses taken: 11 capsules/ day Diet/ meal supplementation: not reported With or w/out gastric acid suppression: no AA given Intervention 4: EC high-dose (Pancrease® 22 capsules) Pancreatin or pancrealipase: pancrealipase Product name: Pancrease®	der Kamer 1958). At the end of the study parents rated the treatments in order of preference. Setting: outpatient paediatrics clinic Randomisation method: not reported Allocation concealment: not reported Blinding: not reported Statistics: a William's ballanced cell design was employed to compensate for possible residual effects. For the stool frequency and side effects data, the scores of each 4-week period were combined into a single score and ranked for each child. Rank scores were analysed by Wilcoxon-Man-Whitney U-statistics. For weight change data a two-tailed paired test was performed	No difference. Data not reported. Treatment preferences High dose (Pancrease® 22) was considered better.	Incomplete outcome data (attrition bias): Low risk (All participants completed the treatments of interest) Selective reporting (reporting bias): Low risk (there were no important or systematic differences between groups in terms of those for whom outcome data were not available) Other bias: Low risk (the comparison groups received the same care apart from the intervention(s) studied; there was no difference in fat intake between the groups; the study used a precise definition of outcome; a valid and reliable method was used to measure stool fat, although the method used to diagnose side effects was unclear; the study had an appropriate time of follow-up; all groups were followed

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		Constituent enzymes: each capsule contains 4,000 USNF lipase units; 25,000 USNF protease units; 20,000 USNF amylase units Type of PERT: EC Formulation: beads Timing of administration: not reported Number of tablets and doses taken: 22 capsules/ day Diet/ meal supplementation: not reported With or w/out gastric acid suppression: no AA given *Interventions with non-EC PERT (Viokase) are not relevant to the protocol			up for an equal length of time) Other information Potential conflict of interest? Measure of fat intake self-reported. Patients on their own diet. Study does report weight change results, but follow-up is <28 days Results for tables 2 and 4 cannot be reported, blurred copy of the paper
Full citation Beker, L. T., Fink, R. J., Shamsa, F. H., Chaney, H. R., Kluft, J., Evans, E., Schidlow, D. V., Comparison of weight-	Sample size n=21 Characteristics Group: children Gender (M/F): 13/ 8 Age (mean±SD): 11.5±3.2 (5 to 28)	Interventions High dose: Pancreatin or pancrealipase: not reported Product name: not reported	Details Procedure: Patients were hospitalized for 9 days, with a 48-h wash out period between regimes. The enzyme dosage was given in combination to	Results Fecal fat excretion (g/24 h) mean±SEM: 10.3±2.4 vs. 15.3±3.7 Fat absorption (%)	Limitations Assessed with Cochrane risk of bias tool: Random sequence generation (selection bias): Low risk (An

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
based dosages of enteric-coated microtablet enzyme preparations in patients with cystic fibrosis, Journal of Pediatric Gastroenterology & Nutrition, 19, 191-7, 1994 Ref Id 346496 Country/ies where the study was carried out USA Study type Open-label cross over clinical trial Aim of the study To evaluate the effectiveness of large doses of lipase in improving the absorption of dietary fat by using and EC microtablet enzyme preparation. Study dates Not reported. Source of funding Funded in part by a grant from the R.W. Johnson Pharmaceutical Research Institute.	Inclusion criteria Diagnosis of CF based on abnormal sweat chloride levels of >60 mEq/L. (Gibson & Cooke). Pancreatic insufficiency for >6 months. >2 years old Exclusion criteria Patients in other study protocols. Patients taking other drugs that could augment the effect of enzymes (antacid, H2, antidiarrheal drugs...).	Constituent enzymes: lipase Type of PERT: EC Formulation: microtablets Timing of administration: not reported Number of tablets and doses taken: 1500U lipase per kg/body weight for meal & 750U lipase per kg/body weight for snack in appropriate combination Diet/ meal supplementation: if necessary high-fat foods given to achieve 100g diet With or w/out gastric acid suppression: no AA given Low dose: Pancreatin or pancrealipase: not reported Product name: not reported Constituent enzymes: lipase Type of PERT: EC	achieve ≥4,000; 12,000 & 16,000 U of lipase to provide the lowest number of capsules possible. Subjects were instructed about the fat content of hospital menu and were supplemented with high-fat foods to achieve an estimated 100g fat diet. A 72-h stool collection was obtained at the end of each dosage regimen. Outcome measures: Stool collections were assessed for fecal fat using the van de Kamer method. Setting: hospital Randomization: simple randomization scheme generated from random digit tables Concealment: not reported Blinding: open-label Statistics: an equivalent to the ANOVA for cross-over trials, the two-sample t test was used. A t test compared the sum of both treatment periods was used to determine if there was treatment effect.	Mean±SEM: 91.2±1.6 vs. 86.2±3.2 Side effects Episodes of constipation or elevations in serum uric acid levels on either enzyme dose were not observed.	appropriate method of randomization was used; the groups were comparable at baseline). Allocation concealment (selection bias): Unclear risk (Unclear if there was appropriate allocation concealment) Blinding (performance bias and detection bias): Unclear risk (Participants were not "blind" to treatment allocation; those administering care and investigators were not "blind" either; however fecal fat is an objective measure) Incomplete outcome data (attrition bias): Low risk (There were no important or systematic differences between groups in terms of those who did not complete treatment). Selective reporting (reporting bias): Low risk (there were no

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		Formulation: microtablets Timing of administration: not reported Number of tablets and doses taken: 500U lipase per kg/body weight for meal & 250U lipase per kg/body weight for snack in appropriate combination Diet/ meal supplementation: if necessary high-fat foods given to achieve 100g diet With or w/out gastric acid suppression: no AA given			important or systematic differences between groups in terms of those for whom outcome data were not available). Other bias: Low risk (the comparison groups received the same care apart from the intervention(s) studied; although fat intake was not standardized there were no significant differences in fat intake between the groups; the study used a precise definition of outcome and a valid and reliable method was used to determine the outcome; the study had an appropriate time of follow-up; all groups were followed up for an equal length of time) Other information Potential conflict of interest. No carry-over effect ($p<0.05$)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Durie, P. R., Bell, L., Linton, W., Corey, M. L., Forstner, G. G., Effect of cimetidine and sodium bicarbonate on pancreatic replacement therapy in cystic fibrosis, Gut, 21, 778-86, 1980 Ref Id 333989 Country/ies where the study was carried out Canada Study type Cross-over Aim of the study To compare the use of cimetidine as adjunt to PERT in a restricted population of adolescent patients with CF and steatorrhoea. Study dates Not reported Source of funding Not reported.	Sample size n=21 Characteristics Age: 10 to 21 years old Gender: not reported Inclusion criteria Patients with CF (diagnosed confirmed by a raised sweat chloride determination >60 mmol) All patients had malabsorption by history Patients on receiving PERT treatment Exclusion criteria Individuals with normal pancreatic function, cardiac disorders, hepatobiliary disease, diabetes or severe pulmonary symptoms.	Interventions Group 1: Pancrealipase alone Pancreatin or pancrealipase: pancrealipase Product name: Cotazym® (not authorized in the UK, but same active principle) Constituent enzymes: not reported Type of PERT: EC Formulation: capsules Timing of administration: not reported Number of tablets and doses taken: 26 capsules/ day (6 capsules per meal & 3 capsules per snack) Diet/ meal supplementation: not modifications made to diet, but food was recorded. Mean intake during study 116±39.9 fat With or w/out gastric acid suppression: no AA given	Details Procedure: Each treatment period consisted of 3 days of equilibration followed by 4 days of stool collection. A registered nurse coordinated the study and provided instructions for the completion of food records, administration of drugs and stool collection. Outcome measure: Stool was analyzed for fat using the Van der Kamer method. A stool sheet was used to record the nature and frequency of bowel movements. Setting: CF clinic at the Hospital for Sick Children, Toronto Randomization method:not reported Allocation method: not reported Blinding: not reported Statistical analysis: Stool fat was analyzed using the ANOVA for cross-classifications (randomized blocks) with subsampling. Faecal outputs of fat were compared by ANOVA for	Results Faecal fat (g/24h) Pancrealipase + cimetidine: 20.3±12.6 Pancrealipase alone: 31.3±15.5 (p=0.01) Faecal fat (% of intake) Pancrealipase + cimetidine: 17.8±9.7 Pancrealipase alone: 27.6±13.3 (p=0.01)	Limitations Assessed with Cochrane risk of bias tool: Random sequence generation (selection bias): Unclear risk (Not reported. Unclear if the groups were comparable at baseline). Allocation concealment (selection bias): Unclear risk (Not reported) Blinding (performance bias and detection bias): Unclear risk (Not reported; however fecal fat is an objective measure, thus blinding may not be very important) Incomplete outcome data (attrition bias): Unclear risk (Of the 21 patients that entered the study, 3 withdrew voluntarily after 3 days (no explanation). Three patients were withdrawn on evidence of poor

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		Group 2: pancrealipase + cimetidine Pancreatin or pancrealipase: pancrealipase Product name: Cotazym® (not authorized in the UK, but same active principle) Constituent enzymes: not reported Type of PERT: EC Formulation: capsules Timing of administration: not reported Number of tablets and doses taken: 26 capsules/ day (6 capsules per meal & 3 capsules per snack) Diet/ meal supplementation: not modifications made to diet, but food was recorded. Mean intake during study 116±39.9 fat. With or w/out gastric acid suppression: cimetadine, supplied as 200g & 300g tablets, give in 4 equal doses (1h after food and at bedtime)	randomized blocks and paired t-test.		drug and diet compliance and inadequate stool collection. One patient withdrew because of a possible complication with cimetidine; unclear if there were important or systematic differences between groups in terms of those who did not complete treatment) Selective reporting (reporting bias): Unclear risk (see withdrawals described above) Other bias: Low risk (the comparison groups received the same care apart from the intervention(s) studied; the study had an appropriate time of follow-up; all groups were followed up for an equal length of time) Other information Important lost to follow-up (15 of 21 completed the study)

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		in a total dose of 20 mg/kg/day			One patient withdraw because of a possible complication with cimetidine.
Full citation Brady, M. S., Rickard, K., Yu, P. L., Eigen, H., Effectiveness and safety of small vs. large doses of enteric coated pancreatic enzymes in reducing steatorrhea in children with cystic fibrosis: a prospective randomized study, Pediatric Pulmonology, 10, 79-85, 1991 Ref Id 346528 Country/ies where the study was carried out USA Study type A prospective randomized cross-over study Aim of the study To evaluate the effectiveness and safety of a relatively large dose (patient's usual dose) vs a small dose (1/4 usual dose)	Sample size n=9 Characteristics Group: children Gender (M/F): 5/ 4 Age (median/ range): 9yr 5mo (6yr 10mo to 10yr 2mo) Inclusion criteria Children with CF (diagnosis established by duplicate sweat chloride measurements of greater than 60 mEq/L, according to Gibson and Cooke). Patients who experienced malabsortion by history and consumed relatively large doses of EC enzymes (eg. >25 capsules/day) Nourished subjects (weight for height > 5th percentile) Serum albumin concentration ≥3.2 g/dl No patient received antibiotics or any drugs known to interfere with	Interventions High-dose: the usual clinically established dose of EC enzyme capsules Pancreatin or pancrealipase: not reported Product name: not reported Constituent enzymes: Type of PERT: EC Formulation: capsules Timing of administration: immediately before meals Number of tablets and doses taken: mean±SE 12±1.2: range 8 to 18 capsules per meal Diet/ meal supplementation: all participants received same amount of daily fat (94±6) With or w/out gastric acid suppression: no AA given	Details Procedure: carried out in 2 consecutive 7-day treatment periods. Each treatment period consisted of 3 days at home (wash-out and recovery period) followed by 4 days of weighted food intake and 72h stool collection in the hospital Outcome measure: all stools were analyzed for fat using the method of van de Kamer Setting: inpatients at the Indiana University Hospital Randomisation method: was done balancing by gender, but details are not reported Allocation concealment: not reported Statistics: mean & SEM calculated for all outcomes, including fat excretion. An ANOVA for cross-over designs was performed to compare large vs low dose. A one-tailed paired t-test was	Results Fecal fat excretion (as % of fat intake) - as % of intake (mean±SEM): 8.7±2.2 vs. 13±3.0; p=0.037 - g/kg/24h (mean±SEM): 0.296±0.093 vs. 0.497±0.126; p=0.039 - g/24h. (mean±SEM): 7.89±1.77 vs. 11.92±2.42; p=0.051	Limitations Limitations assessed with the Cochrane risk of bias tool: Random sequence generation (selection bias): Unclear risk (Not reported. Unclear if the groups were comparable at baseline) Allocation concealment (selection bias): Unclear risk (Not reported) Blinding (performance bias and detection bias): Unclear risk of bias (Not reported, however given the nature of the outcomes it may not have an impact) Incomplete outcome data (attrition bias): Low risk (The groups were comparable for treatment completion)

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of EC pancreatic enzymes. (COMPARISON 2. HIGH DOSE VS LOW DOSE) Study dates Not reported Source of funding Partly funded by Indiana University research grant MO1 RR 00750-15	uric acid metabolism or excretion. Exclusion criteria None reported.	Low-dose: one-fourth of the usual dose of EC enzyme capsules Pancreatin or pancrealipase: not reported Product name: not reported Constituent enzymes: Type of PERT: EC Formulation: capsules Timing of administration: immediately before meals Number of tablets and doses taken: mean±SE 3±0.4: range 2 to 5 capsules per meal Diet/ meal supplementation: all participants received same amount of daily fat (94±6) With or w/out gastric acid suppression: no AA given Treatment details: 7,020 units of lipase	used to determine the significance of the differences between doses within each subject.		Selective reporting (reporting bias): Low risk (The groups were comparable with respect to the availability of outcome data) Other bias: Low risk (the comparison groups received the same care apart from the intervention(s) studied; the study used a precise definition of outcome; a valid and reliable method was used to measure the outcomes; the study had an appropriate time of follow-up; all groups were followed up for an equal length of time) Other information Conflict of interest: not reported Possible indirectness: inpatients only? Only includes patients who experienced malabsortion by history

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Doses non-standardized
Full citation Heijerman, H. G., Lamers, C. B., Bakker, W., Dijkman, J. H., Improvement of fecal fat excretion after addition of omeprazole to pancrease in cystic fibrosis is related to residual exocrine function of the pancreas, Digestive Diseases & Sciences, 38, 1-6, 1993 Ref Id 346581 Country/ies where the study was carried out Netherlands Study type Double-blind, randomised cross-over fashion using single dummy technique Aim of the study To investigate the effect of omeprozole-induced gastric acid inhibition on fecal fat excretion during treatment with a standard dose of	Sample size N = 11 Characteristics Male/Female: 5/6 Age: 20 - 42 All patients had pulmonary involvements and used pancreatic enzyme supplements because of pancreatic insufficiency. 1 patient had insulin-dependent diabetes mellitus. No patient had previous gastrointestinal surgery or renal failure. Inclusion criteria - Patients with a faecal fat excretion of more than 10% during treatment wit pancrease 2 capsules three times a day Exclusion criteria Not reported.	Interventions 2 different modalities for 14 days cross-over (28 days in total). 1) Pancrease 2 caps, 3 per day and omeprozole placebo 2) Pancrease 2 caps, 3 per day and omeprozole 20 mg once in the morning Pancrease: 5000 units lipase, 2900 units amylase, 330 units protease per capsule	Details Pancreatic function tests were performed after an overnight fast. Two basal blood samples with an interval of 10 minutes were taken, followed by a test meal consisting of 200 ml Noridrink (Nutricia, Zoertermeer, The Netherlans) and 200 g yoghurt to which 50 g glucose (to all apart from participant with diabetes) and 2 mmol of synthetic peptide NBT-PAPA, bentitomide has been added. The meal consisted of 16.6 g protein, 20 g fat and 93.8 g carbohydrate (around 622 cal / 2611 J). Omeprozole or matching placebo was given 30 minutes before breakfast while pancrease was taken 3 times a day, one capsule before and one capsule directly after each meal. During last 5 days of each treatment period, all subjects were on their usual diet with a fixed daily fat intake, identical during both	Results Faecal fat excretion (% of daily fat intake): Treat A: Pancreas alone: mean: 22.9, median: 20, range: 12 to 44; vs Treat B: Pancrease + Omeprazole: mean: 18.1, median: 17, range: 4 to 45. Change of faecal fat excretion (%): Mean: 18.8; median: 19; range: -42 to 75. Change in faecal fat excretion = [(B - A)/A]	Limitations Assessed with Cochrane risk of bias tool: Random sequence generation (selection bias): Unclear risk (Method of randomisation unclear; groups were not comparable at baseline because daily intake of fat differed, it was low for 3/11 participants) Allocation concealment (selection bias): Unclear risk (Not reported) Blinding (performance bias and detection bias): Low risk (Double blind) Incomplete outcome data (attrition bias): Low risk (All participants completed treatment) Selective reporting (reporting bias): Low risk (The groups were comparable

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pancrease and its relation with residual exocrine pancreatic function as determined by noninvasive tests. Study dates Not reported. Source of funding Not reported.			treatment periods. On the last 3 days of each treatment period, fat excretion was measured on the last day of each treatment period according to Van de Kamer et al, 1949 method. Randomisation method Unclear Allocation concealment Unclear Statistical analysis Differences in faecal fat excretion were calculated using Wilcoxon's rank-sum test for paired differences.		with respect to the availability of outcome data) Other bias: Low risk (The comparison groups received the same care apart from the intervention(s) studied. The study used a precise definition of outcome. A valid and reliable method was used to determine the outcome. The study had an appropriate length of follow-up. All groups were followed up for an equal length of time). Other information
Full citation Heijerman, H. G., Lamers, C. B., Bakker, W., Omeprazole enhances the efficacy of pancreatin (pancrease) in cystic fibrosis, Annals of Internal Medicine, 114, 200-1, 1991 Ref Id 346607	Sample size n=9 Characteristics Mean age in years: 29 (23-42) Adult patients who had CF with pulmonary and pancreatic involvement. Diagnostic of CF by a positive quantitative sweat test: choride concetration › 60 mmol/l.	Interventions I1. Pancrease low dose Pancreatin or pancrealipase: pancreatin Product name: Pancrease (Cilag, Herentals) Constituent enzymes (per capsule): 5000u lipase, 2900u	Details Procedure: During the last 5 days of each treatment period, all patients were on their usual diet with a fixed daily fat intake, which was identical during each treatment period. On the last 3 days of the fixed daily fat intake a 72h stool collectin was done	Results Fetal fat excretion (% of intake) Comparison 2. High dose vs low dose: I2 vs I1. median: 18 (10-34) vs. 20 (12-44) Comparison 3: PERT vs PERT+AA I3 vs I1:	Limitations Assessed with Cochrane risk of bias tool: Random sequence generation (selection bias): Unclear risk (Method of randomisation unclear; unclear if the groups were comparable at baseline)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Holland Study type Double-blind, placebo-controlled, randomized crossover study Aim of the study The effect of Omeprazole therapy as adjunt to two different doses of Pancrease on fecal fat excretion in adult patients with CF. (COMPARISON 1. AA VS NON-AC) (COMPARISON 2. HIGH DOSE VS LOW DOSE) Study dates Not reported Source of funding Not reported. However Pancrease and matching placebos were provided by Cylag Limited Herentals (Belgium) and Omeprazole and matching placebos by Hässle Mölndal (Sweeden)	Inclusion criteria Patients with a fecal fat excretion of more than 10% during treatment with Pancrease, 2 capsules/ 3 times per day. Exclusion criteria None reported.	amylase, 330u amylase Type of PERT: EC Formulation: microspheres Timing of administration: 3 times per day, divided in aliquots of half the dose just before and after the meals Number of tablets and doses taken: 6 capsules (2 capsules/ 3 times day) Diet/ meal supplementation: not given With or w/out gastric acid suppression: without I2. Pancrease high dose only 4 capsules/ 3 times day Pancreatin or pancrealipase: pancreatin Product name: Pancrease (Cilag, Herentals) Constituent enzymes (per capsule): 5000u lipase, 2900u amylase, 330u amylase Type of PERT: EC	Outcome measure: fat content determined by the method of Van de Kamer Setting: not reported Randomisation method: not reported Allocation concealment: not reported Statistics: Wilcoxon rank-sum test for paired differences	median: 14 (6-32) vs. 20 (12-44) I4 vs I2: median: 9 (4-25) vs. 18 (10-34)	Allocation concealment (selection bias): Unclear risk (Unclear if there was appropriate allocation concealment) Blinding (performance bias and detection bias): Low risk (Participants and those administering care were blinded to treatment allocation, although the authors do not explain how this was done; Unclear if investigators were kept blinded to participants' exposure to the intervention and to other confounding and prognostic factors). Incomplete outcome data (attrition bias): Low risk (All participants completed treatment) Selective reporting (reporting bias): Low risk (Outcome data available for all participants)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		Formulation: microspheres Timing of administration: 3 times per day, divided in aliquots of half the dose just before and after the meals Number of tablets and doses taken: 12 capsules (4 capsules/ 3 times day) Diet/ meal supplementation: not given With or w/out gastric acid suppression: without I3. Pancrease low dose + AA Pancreatin or pancrealipase: pancreatin Product name: Pancrease (Cilag, Herentals) Constituent enzymes (per capsule): 5000u lipase, 2900u amylase, 330u amylase Type of PERT: EC Formulation: microspheres Timing of administration: 3 times per day, divided			Other bias: Low risk (The comparison groups received the same care apart from the intervention(s) studied. The study used a precise definition of outcome. A valid and reliable method was used to determine the outcome. The study had an appropriate length of follow-up. All groups were followed up for an equal length of time). Other information Conflict of interest: not reported Wash out period

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		in aliquots of half the dose just before and after the meals Number of tablets and doses taken: 6 capsules (2 capsules/ 3 times day) Diet/ meal supplementation: not given With or w/out gastric acid suppression: Omeprazole 20 mg/day 30' before breakfast I4. Pancrease high dose + AA Pancreatin or pancrealipase: pancreatin Product name: Pancrease (Cilag, Herentals) Constituent enzymes (per capsule): 5000u lipase, 2900u amylase, 330u amylase Type of PERT: EC Formulation: microspheres Timing of administration: 3 times per day, divided in aliquots of half the dose just before and after the meals			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		Number of tablets and doses taken: 12 capsules (4 capsules/ 3 times day) Diet/ meal supplementation: not given With or w/out gastric acid suppression: Omeprazole 20 mg/day 30' before breakfast			
Full citation Francisco, M. P., Wagner, M. H., Sherman, J. M., Theriaque, D., Bowser, E., Novak, D. A., Ranitidine and omeprazole as adjuvant therapy to pancrelipase to improve fat absorption in patients with cystic fibrosis, Journal of Pediatric Gastroenterology & Nutrition, 35, 79-83, 2002 Ref Id 333998 Country/ies where the study was carried out	Sample size 10 adults and 12 children Characteristics 15 males Adults age: 18 to 36 yo Children age: 6 to 17 yo Inclusion criteria Patients with CF confirmed by a sweat test and pancreatic insufficiency Patients were not receiving other agents to modify intestinal Exclusion criteria Pregnant patients Patients with cholestasis (bilitrrubin concentration pH> 1.5 mg/dl)	Interventions PERT treatment was the same for all patients in the trial: Pancreatin or pancrealipase: pancrealipase Product name: Pancrease® MT10 or MT16 Constituent enzymes: not reported Type of PERT: EC Formulation: microtablet Timing of administration: not reported Number of tablets and doses taken: not reported	Details Procedure:patients were studied at baseline whilst receiving their usual dose of PERT and where needed the dosages were adjusted before adding adjuvant therapy. All patients were changed to Pancrease M10 or M16, equivalent to their usual home dosage and received enzymes from the same lot. Adjuvant therapy was started 3 days before admission. Patients received a controlled diet based on an analysis conducted during 3 days of eating their usual home diets. The diet for	Results Fat absorption* Adults Low dose ranitidine: 84.45, 91.42, 94.7, 97.45, 97.45, 95.52, 72.28, 96.3, 96.55, 86.24 High dose ranitidine: 87.56, 91.87, 88.62, ND, 81.89, 79.88, 81, 97.02, 93.48, 91.11 Omeprazole: 84.72, 90.88, 94.27, ND, 84.45, 88.26, 65.48, 85.13, 92.39, 87.4 Placebo: 75.47, 90.86, 88.59, 89.8, 79.01, 93.76, 60.22, 94.73, 96.21, 80.48 Children	Limitations Assessed with Cochrane risk of bias tool: Random sequence generation (selection bias): Unclear risk (details not reported) Allocation concealment (selection bias): Unclear risk (Unclear if there was adequate concealment allocation) Blinding (performance bias and detection bias): Low risk (Participants and those administering care were kept blinded to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
USA Study type Double-blind placebo controlled crossover study Aim of the study To measure the effect of acid suppressant therapy of fat absorption in patients with CF who received a pH-sensitve, ECM enzyme product Study dates Not reported Source of funding Glaxo-Wellcome, Merck and Ortho-McNeil provided the drugs	Patients with hepatosplenomegaly	Diet/ meal supplementation: diet fat was kept constant, no exact data reported With or w/out gastric acid suppression: there are four intervention conditions Low-dose or high-dose ranitidine: children weighting ≤40 kg were given ranitidine 5 mg/kg or 10 mg/kg daily, divided into 2 equal doses 30 minutes before breakfast and dinner. Children weighting >40 kg and adults received 150 mg or 300 mg twice daily. Omeprazole (adults only): 20 mg daily, 30 minutes before breakfast Placebo	each fat-balance study period was kept constant for fat content and the number of meals and snacks per day. Carmine red. 1,000 mg was administered at the time the controlled diet started, and a second dose of carmine red was administered 72h later. Stool collection started after the first red stool had passed and continued until the second red marker was passed. Outcome measure: Fat absorption was calculated as 72-hour dietary fat intake (g). Quantitative fat analysis was performed according to Van de Kamer method. Setting: inpatients Randomization method: the order of treatment was randomly assigned, although the details were not reported Allocation concealment: not reported Blinding: double-blind, details not reported Statistics: paired t-test.	Low dose ranitide: 87.65, 95.69, 72.38, 75.74, 86.34, 80.85, 89.38, 74.67, 68.15, 63.81, 90.55, 94.69 High dose ranitide: 93.27, 80.5, 86.25, 78.19, 88.02, 61.78, 88.77, 69.84, 69.01, 75.59, 81.31, 94.33 Placebo: 92.24, 72.58, 72.53, 88.5, 88.35, 72.12, 92.51, 85.11, 72.12, 60.85, 75.62, 93.25 *The paper provided raw data. Medians and p values were calculated by the technical team.	treatment allocation, although details on how this was done were not reported; unclear if investigators were kept blinded to participants' exposure to intervention and important confounding and prognostic factors) Incomplete outcome data (attrition bias): Low risk (There were no important or systematic differences between groups in terms of those who did not complete treatment. Data is missing only for 1 adult for the high dose and Omeprazole comparisons). Selective reporting (reporting bias): Low risk (The groups were comparable with respect to the availability of outcome data) Other bias: Low risk (The comparison groups received the same care apart from

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					the intervention(s) studied. The study used a precise definition of outcome. A valid and reliable method was used to determine the outcome. The study had an appropriate length of follow-up. All groups were followed up for an equal length of time). Other information Small population for adult interventions with high-dose ranitidine and omeprazole