Review Article

Pancreatic Enzymes: Appropriate Use in Clinical Practice

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EXTRACT

Pancreatic enzymes are the mainstay treatment of exocrine pancreatic insufficiency related to chronic pancreatitis and post pancreatic surgery. Other potential but controversial uses are treatment of abdominal pain in chronic pancreatitis, treatment of weight loss in advanced pancreatic cancer and for dyspepsia. Appropriate dosages, preparations, adjuvant therapy and schedules of administration for pancreatic enzymes in each indication are addressed and summarized.

Key words : pancreatic enzymes, appropriate use

[Thai J Gastroenterol 2005; 6(3): 158-166]

Exocrine pancreatic insufficiency (EPI) is an important consequence of chronic pancreatitis (CP), post-pancreatic surgery and pancreatic cancer. Among these, EPI due to CP is the most important indication for the use of pancreatic enzymes, followed by post-pancreatic surgery. Although treatment of EPI with pancreatic enzymes seems to be straightforward by replacing the deficient endogenous pancreatic enzymes with sufficient amount of oral pancreatic enzymes, unfortunately many physicians are confused with the indications, appropriate preparations, dosage, schedule and timing of administration of pancreatic enzyme treatment. Other potential uses of pancreatic enzymes are treatment of abdominal pain in CP and treatment of dyspepsia, which are controversial. This article will address all these issues and recommendations will be given.

Preparations of Pancreatic Enzyme in Thailand

Currently, available pancreatic enzyme preparations in Thailand are shown in Table 1.

Indications of Pancreatic Enzyme Therapy

1. Treatment of exocrine insufficiency in CP
2. Treatment of abdominal pain in CP
3. Treatment of exocrine insufficiency following pancreatic surgery
4. Treatment of weight loss in unresectable pancreatic cancer
5. Dyspepsia

Treatment of Exocrine Insufficiency in Chronic Pancreatitis

Pancreas has 10 to 20-fold reserve of exocrine

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Table 1 Pancreatic enzyme preparations in Thailand

Preparation	Type*	Content (USP Units)			Dosage *per* meal to achieve lipase 90,000 USP/#
		Lipase	Protease	Amylase	
Creon 10000	ECM	10,000	37,500	33,200	9 capsules
Combizym	ECT	7,400	26,250	29,050	12 tablets
Combizym compositum	ECT	13,500	47,500	53,950	6-7 tablets
Gaszym	ECT	3,000	12,500	9,960	30 tablets
Enzymet	ECT	3,000	12,500	9,960	30 tablets
Polyenzyme-I	ECT	1,500	6,250	4,980	60 tablets
Polyenzyme-N	ECT	6,000	25,000	19,920	15 tablets

*ECM = enteric-coated microspheres, ECT = enteric-coated tablets
#Dosage calculated by the labeled amount of lipase. Practically, treatment may be started with 1/2 of these dosages (see text for details)

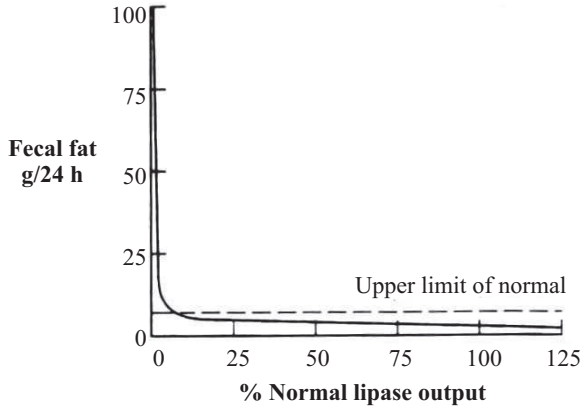

Figure 1 Relationship between lipase output and steatorrhea. Steatorrhea does not occur until lipase output is reduced below 5-10% of normal. (From Ref. 1 with permission)

secretion. Fat maldigestion and steatorrhea do not occur until >90% of exocrine pancreas has been destroyed and lipase secretion is below 5-10% of normal.[1] (Figure 1) In alcoholic CP, it usually takes >10 years after the onset of symptoms of CP to develop severe EPI, while in early-onset and late-onset idiopathic CP are 26 years and 17 years in average, respectively.[2]

Indications of Pancreatic Enzyme Replacement

Pancreatic enzyme should be started when there is >90% reduction of lipase secretion, or clinically, the presence of steatorrhea. In clinical practice, visual inspection of steatorrhea is not sensitive and can detect only 60% of steatorrhea and only 80% of severe steatorrhea (i.e. fecal fat >15 g/24 hr). Stool Sudan III can detect fecal fat only when it exceeds 15 g/day. Furthermore, steatorrhea may be absent in Thai patients with CP even with significant EPI due to the low amount of fat in Thai foods. Thus, the presence of diarrhea or weight loss in CP patients may be enough to warrant treatment of EPI.

Dosage

To abolish malabsorption, the minimal amount of enzymes delivered to the duodenum should be at least 10% of normal enzyme outputs[1]. Clinically, fat malabsorption from lipase deficiency is most critical because it occurs earliest and is least compensated by other enzymes i.e. salivary amylase, gastric proteases and small bowel brush-border peptidases[3]. Practically, if we give the enzyme replacement with sufficient dosage for lipase, the amount of proteases and amylase are usually more than enough.

The normal lower limit of lipase output is 77,000 IU/hour (by using triolein assay as proposed by Mayo Clinic 1). Therefore, for fat malabsorption, lipase 7,700 IU/hr (10% of normal) is required for 4 hours postprandially for each meal or 30,000 IU/meal. This dosage has widely been recommended and quoted by most recommendations and textbooks. However, the most misunderstood point is all commercial pancreatic enzyme preparations currently label their contents in USP (United States Pharmacopoeia) unit or Ph Eur (European Pharmacopoeia), which is approximately 3 times higher than those originally from the triolein assay[4]. Therefore, the exact recommended dose is 90,000 USP or 90,000 Ph Eur of lipase per meal.[5]

Lipase 90,000 USP or Ph Eur can be achieved by different dosages of each commercial enzyme preparation in Thailand (Table 1). Practically, we can start with only $\frac{1}{2}$ of the calculated dose[6] because the actual

amount of enzymes in the preparations are generally higher than the amount labeled (usually ~2 times higher[4]) to ensure the required minimum enzyme activities at the end of the shelf-life. On the other hand, because up to 90% of the ingested lipase can be destroyed by gastric acid, chymotripsin and trypsin, in some cases the dosage may need to increase for 2-4 times if patient fail to improve. Nevertheless, with these recommended dosage, most patients will achieve satisfactory nutritional status, improve diarrhea, steatorrhea and become asymptomatic. Steatorrhea is usually decreased by >50%, though seldom abolished.[7]

It is still unclear whether incomplete abolishing of steatorrhea will have any negative consequence to the patients. Patients with CP have significantly shorter life span[2], partly due to an increased atherosclerotic cardiovascular disease[8] due to an unclear reason but malabsorption and long-term metabolic derangement might be involved. Long-term outcomes of patients who continue to have mild steatorrhea due to inadequate pancreatic enzyme replacement compared to those whose steatorrhea is completely abolished are yet to be elucidated.

Schedule of Administration

Early study by DiMagno *et al.* demonstrated that "prandial schedule" (taking enzymes with meals) is as effective as "hourly schedule" (taking enzyme every 1 hour for 4 hours postprandially) in correcting steatorrhea, but the former is definitely more practical.[9] Recently, a crossover study comparing between schedules of taking enzyme before meals, during meals and just after meals confirmed that taking enzyme during meal is most effective in terms of improving fat digestion, as measured by mixed ^{13}C-triglycerides breath test.[10] Therefore, current recommendation is to take pancreatic enzymes with meals, for example 1 capsule (or tablet) at the beginning of meal, 2 during the meal and 1 immediately after meal.

Enteric-Coating or Conventional Non Enteric-Coating

Lipase is fragile and inactivated at pH <4.0. Besides the destruction by gastric acid, in CP, duodenal pH can fall to below 4.0 postprandially due to the decreased bicarbonate secretion in CP[9]. Thus, most ingested enzymes are destroyed and, no doubt that only 22% of trypsin and 8% of lipase could reach ligament of Treitz[9]. Strategies to overcome this problem are using enteric-coated pancreatic enzymes or adjuvant acid suppression.

Enteric-coated pancreatic enzymes have been designed to release enzymes only when pH is >5.5-6.0. Theoretically, they are expected to pass the stomach without being destroyed by the acid and release the enzymes in the duodenum. However, in studies when adequate dosages of lipase were given, enteric-coated enzymes were shown to be equal or only slightly superior to the non enteric-coated enzymes[11-14] because:

1. In CP, gastric pH will rise above 5.0 in early postprandial period due to the buffering effects of food, but then gastric and duodenal pH will drop to below 4.0 after 40 and 100 minutes, respectively due to decreased bicarbonate secretion[9]. Thus, enteric-coated enzymes may be liberated from their coats in the stomach and subsequently inactivated when the gastric and duodenal pH drop <4.0.

2. Due to the prolonged acidity in duodenum, enteric-coated may release far distally in distal jejunum, ileum or colon, which are not the proper sites for fat digestion.[13,15,16]

3. Enteric-coated preparation in form of tablet (enteric-coated tablet, ECT) may not simultaneously deliver to duodenum with meal, but retain in the stomach[17]. This problem was solved by the development of enteric-coated microspheres (ECM) with appropriate pellet size (1-2 mm), which has been shown to deliver simultaneously with meals to the duodenum.[15] For these reasons, a preferred preparation of pancreatic enzyme is a matter of debate. Physician should consider both advantages and disadvantages of each preparation (Table 2). Discussion with patient will help choosing suitable choice for each patient. Unfortunately, all currently available pancreatic enzyme preparations in Thailand are enteric-coated tablets or enteric-coated microspheres (Table 1).

Adjuvant Acid Suppression Therapy

To overcome lipase inactivation by using acid suppression therapy, postprandial gastric and duodenal pH should be above 4.0 for at least 60 and 90 minutes, respectively[7].

Early studies showed that magnesium-containing antacids and calcium carbonate had no benefit[11] and worsen the steatorrhea due to the formation of magnesium or calcium soaps and precipitation of the bile salts[18]. Aluminium hydroxide antacid has slight benefit but large volume is needed and may dilute the lipase concentration in the lumen.[11,19] Sodium bicarbonate is slightly effective but large dosage of 16 g/

Table 2 Comparison of advantages and disadvantages of nonenteric-coated and enteric-coated pancreatic enzymes (Adapted from 6)

Conventional Non Enteric-Coated Enzymes	Enteric-Coated Enzymes
Advantages	***Advantages***
● Lower cost ● Can use to treat abdominal pain in CP* ● Suitable for patient post gastrectomy or requires long-term acid suppression for other GI diseases (e.g. GERD, etc)	● Patients with marked hyperchlorhydria e.g. cystic fibrosis ● Mixing with meals may be superior (ECM preparation), can be taken without capsule (but must not be crushed or chewed) in patients post gastric bypass surgery or in children ● High content of lipase available, improve patient compliance
Disadvantages	***Disadvantages***
● Patients with hyperchlorhydria e.g. cystic fibrosis (unless adjuvant acid suppression is used) ● Mixing with meal may be inferior, particularly in patient post gastric bypass surgery (except using powder form) ● May affect compliance in children due to large tablet size	● Higher cost ● Cannot use to treat abdominal pain in CP* ● Unsuitable for patient post gastrectomy or requires long-term acid suppression for other GI diseases (e.g. GERD, etc) ● Probability of colonic stricture with high dosage**

*See details in "Treatment of abdominal pain in CP"
**See details in "Side effects of pancreatic enzymes"

day is required.[20]

Adjuvant H_2-receptor antagonists (H_2-RA) which have been shown to improve efficacy of pancreatic enzyme treatment are cimetidine[11,21-25], ranitidine[26] and famotidine[27]. Although some studies failed to show benefit of cimetidine,[20,28] the dosages of lipase in these studies were inadequate. In overall, adjuvant H2-RA will give benefit and abolish steatorrhea in ~50% of cases if increased gastric and duodenal pH >4.0 is achieved.[11]

Adjuvant proton pump inhibitors (PPI) e.g. omeprazole 20 mg/day or lansoprazole 15 mg/day, also showed benefit in reducing steatorrhea in 25-50% of patients with CP or cystic fibrosis[25,29-31].

PPI and H_2-RA have been compared in 1 study and omeprazole was slightly more effective than cimetidine.[25] However, once daily dose of PPI may be more convenient than using H_2-RA 2-4 times a day.

One advantage of adjuvant acid suppression therapy over enteric-coated enzymes is the correction of bile acid malabsorption. In CP, due to the low duodenal pH, micellar phase of bile acid is decreased as a result of bile acid precipitation[32]. This problem can be corrected by only acid suppression therapy, not by using enteric-coated enzymes.

Although adjuvant acid suppression therapy is beneficial, routine use is not recommended due to the cost, safety and drug interactions. It should be used when steatorrhea persists after adequate dosage of conventional enzymes.

Monitoring of the Efficacy of Treatment

Response to the treatment of EPI with pancreatic enzymes may vary case-by-case due to the different in etiology of pancreatic insufficiency (alcoholic or cystic fibrosis), inconsistency of enzyme amounts between lots and different preparations, difference in gastroduodenal acidity in each patient. Thus, monitoring of the efficacy of treatment is essential. Clinical parameters e.g. weight gain, improvement of diarrhea, reduction of stool weight, improvement of abdominal pain and bloating are signs of treatment success. Normalization of fecal fat measured by 72-hour fecal fat after treatment is ideally the best way to determine success but not unavailable in most centers. Monitoring of qualitative microscopic examination of fat globules in stool was found to be almost as sensitive as the 72-hour fecal fat[33] and is possibly another practical way for assessment.

What to Do with Non-Responder

In patients whose symptoms are not improved despite appropriate treatments mentioned above, many possibilities must be considered including, compliance

of the patients, incorrect diagnosis and presence of other non-pancreatic causes of diarrhea and malabsorption. Some conditions have been shown to increase in prevalence in CP e.g. giadiasis[34,35] and small intestinal bacterial overgrowth syndrome, which was found in 25-70% of patients with CP[36-40]. In Thailand, parasitic infestation should be sought and treated if present.

If none of the causes above is identified, acid suppression should be added or adjusted e.g. changing H_2-RA to PPI, increase dosage of PPI, increased dose of pancreatic enzymes for 2-4 times or changing conventional to enteric-coated preparation. Patient referral to special center may be needed.

Treatment of Abdominal Pain in Chronic Pancreatitis

Rational for the use of pancreatic enzymes to treat abdominal pain in CP is based on the proposed theory that human pancreatic secretion is controlled by negative feedback mechanism via CCK-releasing peptide (CCK-RP) in proximal duodenum. (Figure 2) Therefore, an administration of protease-rich pancreatic enzymes will inactivate CCK-RP and subsequently will reduce pancreatic enzyme secretion, reduce pancreatic duct pressure and, hopefully will reduce pain. However, the existence of this feedback mechanism in human is a matter of debate.

There have been 6 randomized studies comparing the efficacy of pancreatic enzymes versus placebo in the treatment of abdominal pain in CP, however the results are conflicting.[41-46] Although meta-analysis of these studies fails to show benefit of pancreatic enzyme over placebo[47], this meta-analysis was criticized on the heterogeneity of the studies[48]. Nevertheless, some experts have given recommendations regarding to the use of pancreatic enzymes for this indication[48,49], (See below).

Appropriate Patients

In a small study by Slaff, et al, pancreatic enzyme was effective in reducing abdominal pain in 9 of 12 patients (75%) with mild to moderate EPI (defined by no steatorrhea) and 8 of 10 patients (80%) with idiopathic CP. In contrast, the efficacy was poor (2 of 8 patients, 25%) in patients with severe EPI (presence of steatorrhea) and 3 of 10 patients (30%) with alcoholic CP.[41] Recommendation from some authorities (based on this small study) is to use in patients with mild to moderate "small duct" idiopathic CP, not in severe "large duct" alcoholic CP.[48,49]

Type of Pancreatic Enzyme Preparation

From the 6 studies mentioned above, 2 studies using conventional non enteric-coated enzymes revealed benefits of pancreatic enzymes on abdominal pain[41,42], while the 4 studies using enteric-coated did not.[43-46] One of the possible reasons is feedback mechanism was believed to exist in only the proximal duodenum. Thus, only conventional non enteric-coated enzymes are capable to inhibit this feedback because most enteric-coated enzymes have been shown to release far in jejunum or ileum.[13,15,16]

In Thailand, conventional non enteric-coated enzyme is unavailable. Theoretically, we may apply by

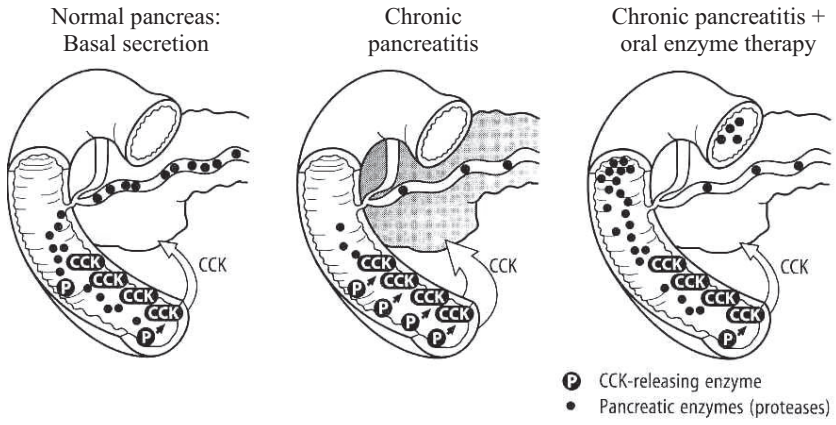

Figure 2 Feedback control mechanisms of pancreatic secretion in duodenum in healthy subject, chronic pancreatitis and effects of pancreatic enzyme replacement (From: Owyang C. Chronic pancreatitis. In:Yamada T, Alpers DH, Laine L, Owyang C, Powell DW, editors. Textbook of gastroenterology 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1999: 2151-77 with permission)

using enteric-coated enzymes with potent acid suppressant (i.e. PPI) to make the enzyme released in the stomach and duodenum. However, this suggestion is based on only the physiology basis of pancreatic enzymes, thus it should be tested in further clinical study.

Dosage and Duration

Recommendation dosage of pancreatic enzyme treatment for pain in CP is protease 25,000-50,000 U/meal for at least 6-8 weeks. If patients do respond, continue treatment for 6 months is recommended. After 6 months of pain improvement, treatment can be stopped and approximately half of the patients will continue being pain-free but the rest will experience relapse, which warrants indefinite pancreatic enzyme treatment.[49]

Treatment of Exocrine Insufficiency following Pancreatic Surgery

Pancreatic surgery is indicated in some patients with CP and intractable pain, acute pancreatitis with infected pancreatic necrosis and various types of pancreatic tumors. EPI following pancreatic surgery is an important consequence but may be difficult to predict since it depends on many factors such as:

1. Underlying pancreatic diseases

1.1 Degree of preoperative EPI Patients with CP are more likely to have EPI after surgery than patients with other pancreatic diseases

1.2 Duration of diseases before surgery Patients with longer duration of EPI before surgery (e.g. CP) may have more compensatory mechanisms to prevent malabsorption (i.e. increased gastric lipase activity and shifting of the site of digestion from duodenum to distal intestine) than patients with diseases with short duration i.e. pancreatic cancer whose functional adaptation is limited.

2. Type of surgery

2.1 Resection vs. drainage surgery Most studies of CP showed that postoperative EPI is less common after drainage surgery than resection. Moreover, many studies even demonstrated improvement of pancreatic function after drainage surgery

2.2 Extent of resection In normal pancreas, the presence of proximal 40% of pancreas is enough to maintain maximal enzyme secretion. In CP, EPI occurs differently (19-55%) depends on type and extent of resection. 50 (Table 3)

Test of Exocrine Insufficiency following Pancreatic Surgery

Direct pancreatic function tests, either secretin- or CCK-stimulation are the best tests but usually unavailable and not feasible in patients after Whipple's operation. Indirect pancreatic function tests e.g. fecal elastase, fecal chymotrypsin, pancreaolauryl or bentiromide test are more feasible. In case these tests are unavailable (for example, in Thailand), test of fecal fat for steatorrhea may be enough although not sensitive. In practical point of view, the presence of diarrhea and weight loss after pancreatic resection should warrant physicians for EPI and a trial of pancreatic enzyme replacement is reasonable.

Dosage, Preparation and Schedule of Pancreatic Enzyme Replacement[51,52]

Dosage of pancreatic enzyme replacement after pancreatic surgery is similar to the dosage for EPI in CP. However, best preparation and schedule of administration are difficult to conclude due to very few comparative studies. Nevertheless, some practical guides are:

1. Whipple's operation Because gastric capacity and mixing ability may be impaired due to antrectomy, recommendation is to take ECM without gelatin capsule. To prevent premature dissolution of the enteric-coat, the microspheres must be sprinkled on acidic food e.g. yogurt or juice and swallowed without chewing. Alternative choice is conventional nonenteric-coated enzyme in powder form (unavailable in Thailand) with H_2-RA or PPI.[52]

Table 3 Pre- and postoperative frequency of steatorrhea in patients with CP undergoing pancreatic resections 50

Surgical procedure	N	Steatorrhea			
		Preoperative		Postoperative	
		N	%	N	%
40-80% distal resection	53	2	3.7	10	19.0
80-95% distal resection	77	7	9.0	29	37.6
Whipple's operation	19	1	5.2	10	55.0

2. Pylorus-preserving pancreaticoduodenectomy (PPPD) or duodenal-preserving resection of pancreatic head (Beger's operation) Theoretically with these operations, gastric mixing capacity would be preserved, thus any preparation and schedule of enzyme replacement would be effective. However, one study showed that in these types of surgery, gastric transit of the ECM was markedly delayed than the food, caused impaired mixing and reduced the efficacy of ECM[53]. Therefore, some authors recommended using conventional nonenteric-coated enzyme in powder form (unavailable in Thailand) with H_2-RA or PPI instead of ECM.[52]

3. Drainage procedure or distal pancreatectomy Since the stomach and duodenum are left intact, any preparation and schedule of enzyme replacement would be effective.

4. Total pancreatectomy To ensure best mixing with food and maximize the enzyme activity, recommendation is to take ECM granules (without gelatin capsule) or conventional nonenteric-coated enzyme in powder form (unavailable in Thailand) with H_2-RA or PPI.[52]

Treatment of Weight Loss in Unresectable Pancreatic Cancer

Patients with unresectable pancreatic head cancer may be further deteriorated by the EPI from the obstructed pancreatic duct. Study by Bruno *et al*.[54] showed that pancreatic enzyme replacement could improve weight loss in these patients. Interestingly, recent study in murine pancreatic cancer showed that pancreatic enzyme replacement could prolong survival of these mice.[55] Thus, currently it may worth trying pancreatic enzyme replacement in patients with unresectable pancreatic head cancer.

Treatment of Dyspepsia

Dyspepsia is another widely claimed indication for the use of pancreatic enzymes. In patients with CP, EPI can manifest as dyspepsia (from maldigestion). Thus, pancreatic enzyme replacement may improve dyspepsia in CP patients. However, efficacy of pancreatic enzymes in patients with dyspepsia from other GI diseases e.g. functional dyspepsia is unclear. There were a few small open-labeled studies on the use of pancreatic enzymes in various GI diseases with dyspepsia and showed some benefit of pancreatic enzymes. Thus, using pancreatic enzymes for treating non-pancreatic causes of dyspepsia is not proven.

Table 4 Side effects of pancreatic enzymes

Soreness of mouth
Perianal irritation
Abdominal pain
Abdominal distention
Diarrhea
Constipation (in infants)
Hyperuricemia
Folic acid deficiency
Allergy to porcine protein
Hypersensitivity reactions following inhalation (powdered forms)
Fibrosing colonopathy (colonic stricture)

Side Effects of Pancreatic Enzymes

Side effects of pancreatic enzymes are summarized in Table 4[56] and most are minor. Pancreatic extracts will form insoluble complexes with folic acid[57], thus long-term use can cause folate deficiency. Hyperuricosuria was found in cystic fibrosis children treated with high doses enzymes.[58,59] The most important complication is fibrosing colonopathy or colonic strictures, which have been described since 1994[60-62]. It usually associates with high doses enzymes in cystic fibrosis children, although cases of fibrosing colonopathy in adults with or without cystic fibrosis have been reported.[63,64] Relative risks of fibrosing colonopathy were 10 folds with a dose of lipase 24,000-50,000 U/kg/day and 200 folds with a dose >50,000 U/kg/day[65]. Thus, current consensus on the use of pancreatic enzyme supplements in cystic fibrosis recommended the dosage of lipase not exceed 10,000 U/kg/day.[65]

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