



USE OF PANCREATIC ENZYME SUPPLEMENTS FOR PATIENTS WITH CYSTIC FIBROSIS IN THE CONTEXT OF FIBROSING COLONOPATHY

Introduction

Although pulmonary involvement is the major morbidity for most individuals with cystic fibrosis (CF), these patients also have a variety of gastrointestinal problems.^{1,2} In 1994, the first colonic strictures were reported in patients with CF in the United Kingdom, Europe, and the United States, and these appeared to be temporally related to the introduction of high-strength pancreatic enzyme supplements (HSPE).³⁻⁶ A spectrum of intestinal involvement has been observed. The term "fibrosing colonopathy" has been coined to include the pre-stricture state as well as the presence of true strictures. Between, January, 1990, and December, 1994, a total of 35 cases of colonic stricture, confirmed by histology at surgery, were reported to the U.S. Cystic Fibrosis Foundation (CFF). The CFF organized a Consensus Conference in March of 1995 in conjunction with the U.S. Food and Drug Administration to examine use of pancreatic enzymes in patients with CF, and to comment on the diagnosis and management of patients at risk of developing fibrosing colonopathy. What follows does not reflect any opinions regarding standards of care prior to the date of the conference.

Treatment of Pancreatic Insufficiency

Ninety-three percent of patients in the U.S. CFF Patient Registry are treated with pancreatic enzyme supplements.⁷ Since pancreatic enzyme supplements were available prior to the 1938 Food, Drug and Cosmetic Act, the usual dosing, efficacy and safety studies were never performed. Few guidelines have been published concerning dosing of pancreatic enzymes, and there is scant literature on adverse events related to enzyme use.

Most published studies have used the three-day fecal fat method to study the efficacy of pancreatic enzyme supplements.⁸⁻¹⁷ The majority of these studies did not include HSPE and most express enzyme dose in terms of capsules per day rather than dose per meal. The numbers of patients studied were small. The range of fecal fat results is wide, indicating great individual variation in response (Table 1). Notably, very few studies have been done on young infants, and most involve older subjects. Thus, the conference participants have come to the following consensus concerning enzyme dosing which is based on limited scientific evidence.

Diet

Pancreatic insufficient patients should consume a high-calorie diet with unrestricted fat which is appropriate for age and clinical status. Additional calories will be required for catch-up growth. A nutritional assessment should be performed regularly as a component of routine care of patients with CF, and additionally, when dosing of pancreatic enzyme replacement is altered.¹⁸

Enzyme Dosing

Infants may be given 2,000-4,000 lipase units per 120 ml of formula or per breast feeding.¹⁸ This provides approximately 450-900 lipase units per gram fat ingested (based on 4.5 grams of fat per 120 ml standard cow's milk-based infant formula). Dosing enzymes per gram of fat ingested provides consistent guidelines for all ages. In general, patients will need 500-4,000 lipase units per gram of fat ingested per day (mean = 1,800 lipase units per gram of fat per day).¹⁹ This system of calculating the dose takes into account the fact that fat intake is high relative to body weight in infancy, but decreases with time. On average, infants ingest 5 grams of fat per kilogram of body weight per day, whereas adults tend to ingest about 2 grams of fat per kilo per day. Dosing enzymes according to how much fat is eaten per meal is more likely to mimic the body's own response of adjusting pancreatic enzyme excretion relative to how much fat is present in a meal.

Alternatively, a weight-based scheme for pancreatic enzyme dosing may be used. Although less physiologic, this method is a practical way to determine the number of enzyme capsules needed per meal. This avoids shifting dosing schedules which may be confusing for some caretakers, (e.g., daycare, schools, children in joint custody) or may be difficult for some patients to understand. Weight-based enzyme dosing should begin with 1,000 lipase units/kg/meal for children less than age four years, and at 500 lipase units/kg/meal for those over age four. Enzyme doses expressed as lipase units/kg/meal should be decreased in older patients since they weigh more but tend to ingest less fat per kilogram. Usually, half the standard dose is given with snacks. The total daily dose should reflect approximately three meals and two to three snacks per day.

If symptoms and signs of malabsorption persist, the dose may be increased by the CFF Care Center staff. Patients should be instructed not to increase the dose on their own. There is great interindividual variation in response to enzymes; therefore, a range of doses is suggested. Changes in dose or product may require an adjustment period of several days. If doses exceed 2,500 lipase units/kg/meal, or 4,000 lipase units/gm fat/day, further investigation is warranted (see section on Management of the Patient with a Poor Response to Therapy). Since it is unknown whether doses between 2,500 and 6,000 lipase units/kg/meal or doses >4,000 lipase units/gm fat/day are truly safe, doses above 2,500 lipase units/kg/meal (4,000 lipase units/gm fat/day) should be used with caution and only if they are documented to be effective by three-day fecal fat measures which indicate a significantly improved coefficient of absorption.

Doses above 6,000 lipase units/kg/meal have been associated with colonic strictures in children less than twelve years of age, whether standard strength enzymes or HSPE were taken.⁶ Patients currently on higher doses (>2,500 lipase units/kg/meal or 4,000 lipase units/gram fat ingested/day) should be evaluated and either immediately decreased, or titrated down to a lower dosage range.

Enzyme Products

Most products are capsules which contain enteric-coated microencapsulated enzymes. These may be either microtablets ("MT"; all pellets are the same size) or microspheres (heterogeneous sizes). In this

document, the term microcapsule will be used as a generic term to describe both microtablets and microspheres. The enteric coating prevents inactivation of enzymes in the acidic gastric environment. The dissolution profile of generic microcapsules may not be equivalent to proprietary brands despite identical enzyme content.^{20,21} Patients should receive only the product brands prescribed by their CFF Care Center.²⁰ Since some products contain pancreatin while others contain pancrelipase, the ratio of proteases to lipase is not the same in all brands. It is uncertain if this is clinically relevant. The U.S. Pharmacopeia requirements state that enzyme products may contain no less than 90% of the amount stated on the label, but do not set an upper limit for the contents. Capsules are often overfilled to compensate for enzyme degradation during storage.²¹

Administration of Supplements

Small children may be unable to swallow whole capsules. Capsules may be opened and the contents mixed with a small quantity of applesauce or another non-alkaline food. However, the microcapsules cannot be crushed or allowed to sit in food as disruption of the enteric coating will lead to inactivation of the enzymes. Pancreatic enzymes should be stored in a cool, dry place and checked regularly for expiration dates.

Management of Patients With a Poor Response to Therapy

A poor response to therapy can be defined as continued abdominal complaints (such as bloating; flatus; abdominal pain; loose, frequent stools or overt diarrhea) along with symptomatic steatorrhea (bulky, oily, foul stools) and/or poor growth despite treatment with pancreatic enzymes. Abdominal pain alone does not indicate the need for an increase in enzyme dosage. Before increasing the enzyme dose above the recommended range, one should consider factors which may cause these symptoms, but which will not respond to increasing the enzyme dose (Tables 2 and 3).

Dietary Factors

Dietary factors may lead to a poor response. In younger children, excessive juice intake can cause loose stools due to carbohydrate malabsorption.²² Many parents are unaware that enzymes need to be taken before milk (i.e., they do not think of a liquid as a food) or other small snacks.

Furthermore, lactose intolerance can cause symptoms of malabsorption. "Grazing" food behavior can make enzyme dosing difficult; therefore, discrete meals and snacks are recommended. "Fast food" or other high-fat meals may cause unexpected, temporary changes in stool pattern which do not warrant long-term changes in enzyme dosage.

Adherence Issues

Psychosocial resistance and lack of adherence by choice will result in ongoing malabsorption.²³ Toddlers may willfully refuse enzymes, and this behavior may be amplified in chaotic households or if there are multiple meal givers. School-age children and teens may not take enzymes because of anger about having a chronic disease or a desire to appear "normal." Teenage girls may discover that they receive positive reinforcement by remaining slim, and that it is easy to do so if they do not take their enzymes.

Adjunctive Therapies

Patients with CF who are pancreatic insufficient do not produce the high-volume bicarbonate-rich pancreatic secretion required to neutralize gastric acid. Acidity in the gastrointestinal tract may prevent or retard dissolution of enteric-coated microcapsules.²⁴ Numerous studies have examined the effect of alkalization of the duodenal contents by bicarbonate or drugs that inhibit gastric acidity.²⁵⁻²⁸ These agents may be useful adjuncts in the management of patients with poor response to therapy. Occasionally, use of non-enteric coated pancreatic powders in combination with enteric-coated enzymes, giving some of the total number of capsules at mid-meal, or prescribing a brand of enzyme with a different dissolution profile (e.g., microspheres versus microtablets), may be helpful.

Other Factors

Factors other than abnormal intestinal pH may affect nutrient absorption in patients with CF. Abnormal gastric and intestinal motility, a reduction in the bile acid pool, precipitation of bile acids, and thick, tenacious intestinal mucins may contribute to malabsorption despite provision of adequate amounts of pancreatic enzymes.

Concurrent gastrointestinal problems unrelated to CF may cause symptoms of malabsorption which will not respond to increasing the enzyme dose (Table 3). These diagnoses should be considered if patients do not respond to usual therapy.

Diagnosis and Management of Fibrosing Colonopathy

Definition and Diagnosis

The term fibrosing colonopathy describes a condition associated with ingestion of large quantities of pancreatic enzyme supplements. At its most advanced, this condition leads to colonic strictures. Fibrosing colonopathy should be considered in patients with CF who have evidence of obstruction, bloody diarrhea or chylous ascites, as well as in patients who have a combination of abdominal pain, ongoing diarrhea and/or poor weight gain. Patients at highest risk include those who are less than twelve years of age, have taken >6,000 lipase units/kg/meal of pancreatic enzymes for greater than six months, have a history of meconium ileus or distal intestinal obstruction syndrome, have had any intestinal surgery or have a diagnosis of inflammatory bowel disease.³⁻⁶ While the definitive diagnosis can only be made by microscopic evaluation of surgical resection specimens, overt strictures can be demonstrated by barium enema prior to laparotomy.

The pre-stricture lesion is more difficult to define. A barium enema is the most reliable method for diagnosing fibrosing colonopathy. A contrast enema which shows colonic shortening, focal or extensive narrowing and a lack of distensibility is highly suggestive. Bowel wall thickening alone is not diagnostic.²⁹ Endoscopy may show an erythematous mucosa and areas of narrowing, either proximally in the ascending or transverse colon or involving the entire colon. Multiple forcep-pinch biopsies are recommended. Biopsies which demonstrate fibrosis of the lamina propria are strongly suggestive of the diagnosis. Supportive evidence on biopsy includes inflammation with eosinophils, focal neutrophilic cryptitis and apoptosis. Special stains for tyrosine hydroxylase, neuron specific enolase and acetylcholinesterase are recommended, since some surgical specimens have demonstrated ganglion cells in the lamina propria.³⁰

Some investigators have been able to detect bowel wall thickening with ultrasound, although there is not universal agreement on the range of normal in patients with CF. The presence of ascites is highly suggestive of fibrosing colonopathy. In one study, sonographic evidence of decreased bowel wall thickness occurred after pancreatic enzyme doses were lowered.³¹

Treatment

Patients with fibrosing colonopathy should have the enzyme dosage reduced to within the recommended range of 500-2,500 lipase units/kg/meal. Concurrent diagnoses should be considered in patients who have ongoing abdominal symptoms, and medical adjuncts should be employed as described above. Adequate nutritional support must be maintained in these patients. In some cases, enteral elemental feeding or total parenteral nutrition may be warranted. Patients whose nutritional status cannot be maintained, those showing evidence of obstruction, or those with uncontrollable bloody diarrhea or chylous ascites, will need surgical intervention.

Since the natural history of fibrosing colonopathy remains unknown, patients who have not required surgery should be monitored closely. Some patients may be at risk to progress to stricture formation. It is uncertain whether regression of fibrosing colonopathy occurs.

Goals for Future Research

The occurrence of fibrosing colonopathy has stimulated clinical and basic research questions. The following are areas which the panel felt needed further investigation (Table 4).

Basic Research

Investigations to define the pathogenesis of fibrosing colonopathy are strongly recommended. It was noted that investigators are already developing animal models to attempt to evaluate the pathogenesis of the colonic lesion. Appropriate animal models could be used to evaluate product formulations, the various enzymes, their coatings, and whether or not other contaminants within the enzyme products are responsible for the lesion.

The complex nature of porcine enzyme extracts should be examined in more detail. In addition to the twenty or more digestive enzymes, it was recognized that these crude enzyme extracts contain many other potentially toxic biologically active peptides and/or growth factors. Some factors may be fibrogenic when released in the colon. It was recognized that the pharmaceutical industry may have data on file concerning the various factors that are present in enzyme preparations. The industry is encouraged to divulge these data. Research concerning the biologic and pathologic

effects of some of these preparations is encouraged. The significance of the differing ratios of lipase:amylase:protease in different products should be explored.

With respect to the limitations of existing enzyme preparations, it was recognized that "better" products should be developed. Factors that should be taken into account include the mechanism and site of release of microcapsule preparations and the intestinal environment of patients with CF (intestinal pH, bicarbonate, abnormal intestinal mucins, reduced bile acid pool, the effect of precipitable bile acids, etc.). Alternative enzyme products such as acid stable lipases should be evaluated in more detail.

Non-invasive, quantitative tests of exocrine pancreatic function should be developed. In addition, non-invasive tests capable of determining both the efficacy and fate of orally ingested pancreatic enzyme supplementation are urgently needed. In order to validate non-invasive tests, appropriate invasive tests should be refined; these would serve as the "gold standard" for assessing non-invasive tests of pancreatic function and of the efficacy of enzyme therapy.

Clinical Research

The case-control studies which have been conducted in the United Kingdom and the United States will help to evaluate which factors put patients at risk to develop fibrosing colonopathy.

It was concluded that predictive markers of the "early lesion" of fibrosing colonopathy should be developed. In this regard, longitudinal evaluation of identified cases (particularly those with an "early lesion") was encouraged. Evaluation of the effects of pancreatic enzyme therapy in non-CF pancreatic insufficient patients would also be helpful. Hirschsprung disease, or a secondary complication such as intestinal neuronal hyperplasia were identified as potential clues to the etiopathogenesis of fibrosing colonopathy.

Since preliminary studies suggest a higher prevalence of Crohn's disease in CF, studies concerning the possible relationship between inflammatory bowel disease and enzyme therapy should be entertained. The possibility that this lesion is due to an immune complex disease was entertained.

Clinical studies to evaluate the dissolution characteristics of microcapsular pancreatic enzymes

within the intestine were considered to be an important area of clinical investigation.

Sensitive and reliable diagnostic tools to identify fibrosing colonopathy (imaging techniques, histological assessment, or biochemical tests) require further evaluation and validation. CFF Care Centers which have identified large numbers of cases are encouraged to collaborate. Endoscopic ultrasound was promoted as a specific example of a novel diagnostic technique capable of assessing the intestinal wall. Histologic definitions for diagnosis of fibrosing colonopathy should be standardized.

Additional insights into this condition would be gained by monitoring patients who have previously received high-strength, high-dose pancreatic enzymes but remain asymptomatic.

Behavioral studies designed to evaluate patient response and ability to cope with the adjustments to drug dosages are encouraged as are studies to evaluate adherence to therapy. Techniques designed to improve adherence should be evaluated.

Conclusion

Although the mechanism of injury is unknown, it is now clear that ingestion of high doses of pancreatic enzymes can lead to adverse gastrointestinal events. Until future research gives us more specific answers, physicians must balance the imperfect art of pancreatic enzyme dosing with the need to control malabsorption, since normal nutritional status and growth remain a goal for all patients with CF.

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TABLE 1
EXCERPTED DATA FROM PANCREATIC ENZYME DOSING STUDIES

Ref #	Country	n (M)	Age in years	Enzyme brand (thousands of lipase units) ¹	Dose	coefficient of absorption (range) ²
8	USA	21 (13)	3-27	Pancrease MT ³ Pancrease MT ³	500 lipase units/kg/meal 1500 lipase units/kg/meal	86.2 (31-99) 91.2 (71-100)
9	USA	9 (5)	7-10	Pancrease (4) Pancrease (4)	10 capsules/day 42 capsules/day	87 (69-96) 91.3 (79-98.6)
10	Australia	7 (6)	9-14	Pancrease (4) Pancrease (4)	21 capsules/day (39-51) 45 capsules/day (18-28)	82 (57-95) 90 (78-95)
11	UK	38 (33)	15 mos - 27 yrs.	Creon (8) Pancrease HL (25)	"usual dose" (no less than 12 capsules/day) 1/3 "usual dose"	84 (±10) 83 (±9)
12	UK	19 (?)	6-20	Pancrease (5) "usual dose" Pancreat ⁴ (7.7) Pancrex V Forte (5.6) Creon (8)	18 capsules/day (6-40) 81 (34-94) } adjusted so lipase dose } is equal to "usual dose"	87 24-95) 74 (52-93) 85 (56-94)
13	Italy	73 (30)	4-14	Pancrease (4) (based on fat per meal)	4-57 capsules/day	"<10 - >25"
14	USA	21 (10)	3-27	Pancrease (4) Creon (8)	13 capsules/day (10-29) 9 capsules/day (7-18)	81 (±2.7) 81 (±3.1)
15	UK	10 (?)	(not stated)	Creon (8) Pancrease HL (25)	25 capsules/day (15-45) 9 capsules (5-18)	91 (77-92) 91 (83-94)
16	UK	18 (?)	5-14	Nutrizym GR (10) Nutrizym 22 (22)	30 (15-100) ⁵ 15 (8-80) ⁵	76 (9-92) 91 (57-97)
17	USA	8 (4)	7-14	Pancrease (4) (before meals) Pancrease (4) (during meals)	22 capsules/day (4-37) 22 capsules/day (4-37)	92.7 (±1.4) 91.6 (±1.4)

¹Dose is as stated on the label. Enzyme capsules may be overfilled (see re. #21).

²Coefficient of absorption = grams of fat excreted/grams of fat eaten x 100. In some instances results expressed as % excreted; these were converted to % absorbed for the sake of uniformity. If a standard error was reported without a range, this is listed as "+-".

³Doses given as any combination of Pancrease MT-4, MT-10, and AMT-16 which provided the per kilo dose with the least number of capsules.

⁴Non-enteric coated Pancreat; all other products in this table are enteric-coated.

⁵Number of capsules per day implied in the text but not explicitly stated.

TABLE 2
FACTORS CONTRIBUTING TO A POOR RESPONSE TO
PANCREATIC ENZYME THERAPY

Enzyme Factors
Outdated prescription
Enzymes not stored in cool place
Dietary Factors
Excessive juice intake
Parental perception that enzymes are not needed with milk or snacks
"Grazing" eating behavior
High fat "fast foods"
Poor Adherence to the Prescribed Enzyme Regimen
Toddler willful refusal
Chaotic household/multiple mealgivers
Anger and/or desire to be "normal"
Teenage girls' desire to be slim
Acid Intestinal Environment
Poor dissolution of enteric coating
Microcapsule contents released all at once
Concurrent Gastrointestinal Disorder (see Table 3)

TABLE 3
SOME CONCURRENT GASTROINTESTINAL DISORDERS
WHICH MAY CAUSE MALABSORPTION WHICH WILL NOT
RESPOND TO INCREASING ENZYME DOSE

DIAGNOSIS	EVALUATION
Lactose malabsorption	Stool clinitest, breath test (lactose)
Enteric bacterial infection	Stool WBC, hematest, culture
Parasites, especially giardiasis	Stool for ova and parasites; string test, duodenal aspirate
Bacterial overgrowth of small intestine	Breath test (glucose)
Biliary disease / cholestasis	Alkaline phosphatase, GGT, ultrasound, DISIDAscan, cholangiogram
Pseudomembranous colitis	Stool WBC, hematest, <i>C. difficile</i> toxin titer
Celiac disease	Small bowel biopsy, anti-endomysial and / or antigliadin antibodies
Short bowel syndrome	Surgical history
Crohn's disease	Stool WBC, hematest, contrast radiographs, colonoscopy and / or endoscopy and biopsy

TABLE 4
POTENTIAL AREAS FOR FUTURE RESEARCH

BASIC RESEARCH	CLINICAL RESEARCH
<p>Animal Models of Pathogenesis types of preparations coating of microcapsules effects of enzymes</p> <p>Pancreatic Enzymes composition effects</p> <p>Development of "Better" Enzymes acid-resistant bile-salt independent</p> <p>Tests of Efficacy and Fate of Pancreatic Enzyme Therapy non-invasive invasive</p>	<p>Case-control Studies (UK and US)</p> <p>Clinical Clues to Etiopathogenesis predictive markers of "pre-stricture" lesion</p> <p>longitudinal evaluation of identified cases</p> <p>Fate and Dissolution of Microcapsular Preparations dosing study: HSPE vs. low strength at same dose dissolution in vivo</p> <p>Diagnosis of Fibrosing Colonopathy imaging techniques endoscopic ultrasound histology other</p> <p>Behavioral Aspects of Enzyme Therapy</p>

REFERENCES

1. Park RW, Grand RJ. Gastrointestinal manifestations of cystic fibrosis: a review. *Gastroenterology* 1981; 81:1143-1161.
2. Borowitz D. Pathophysiology of gastrointestinal complications of cystic fibrosis. In: Fiel SB, ed., *Cystic Fibrosis - On the Brink of a New Era. Seminars Respir Crit Care Med* 1994; 15:391-401.
3. Smyth RL, vanVelzen D, Smyth AR, Lloyd DA, Heaf DP. Strictures of ascending colon in cystic fibrosis and high-strength pancreatic enzymes. *Lancet* 1994; 343:85-86.
4. Oades PJ, Bush A, Ong PS, Brereton RJ. High-strength pancreatic enzyme supplements and large-bowel stricture in cystic fibrosis. Letter to the Editor. *Lancet* 1994; 343:109.
5. Campbell CA, Forrest J, Musgrove C. High-strength pancreatic enzyme supplements and large-bowel stricture in cystic fibrosis. Letter to the Editor. *Lancet* 1994; 343:109-110.
6. Freiman J, FitzSimmons SC. Colonic strictures in patients with cystic fibrosis: Results of a survey of 114 CF care centers in the US. *J Pediatr Gastroenterol Nutr* 1995; (in press)
7. FitzSimmons SC. The changing epidemiology of cystic fibrosis. *J Pediatr* 1993; 122:1-9.
8. Beker LT, Fink RJ, Shamsa FH, et al. Comparison of weight-based dosages of enteric-coated microtablet enzyme preparations in patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1994; 19:191-197.
9. Brady MS, Rickard K, Yu PL, 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. *Pediatr Pulmonol* 1991; 10:79-85.
10. Robinson PJ, Sly PD. High dose pancreatic enzymes in cystic fibrosis. *Arch Dis Child* 1990; 65:311-315.
11. Morrison G, Morrison JM, Redmond AOB, et al. Comparison between a standard pancreatic supplement and a high enzyme preparation in cystic fibrosis. *Aliment Pharmacol Ther* 1992; 6:549-555.
12. Beverley DW, Kelleher J, MacDonald A, Littlewood JM, Robinson T, Walters MP. Comparison of four pancreatic extracts in cystic fibrosis. *Arch Dis Child* 1987; 62:564-568.
13. Costantini D, Padoan R, Curcio L, Giunta A. The management of enzymatic therapy in cystic fibrosis patients by an individualized approach. *J Pediatr Gastroenterol Nutr* 1988; 7 (suppl 1):S36-S39.
14. George DE, Pinero R, Miller AB, Toskes PP, et al. Comparison of two pancreatic enzyme supplements in patients with cystic fibrosis. *Adv in Therapy* 1990;7:109-118.
15. Morrison G, Morrison J, Redmond A, Byers C, McCracken K, Dodge JA. Pancreatic enzyme supplements in cystic fibrosis. *Lancet* 1991; 338:1596-1597.
16. Bowler IM, Wolfe SP, Owens HM, Sheldon TA, Littlewood JM, Walters MP. A double blind lipase for lipase comparison of a high lipase and standard pancreatic enzyme preparation in cystic fibrosis. *Arch Dis Child* 1993; 68:227-230.
17. Brady MS, Rickard K, Yu PL, Eigen H. Effectiveness of enteric coated pancreatic enzymes given before meals in reducing steatorrhea in children with cystic fibrosis. *J Am Diet Assoc* 1992; 92:813-817.
18. Ramsey BW, Farrell PM, Pencharz P, and the Consensus Committee. Nutritional assessment and management in cystic fibrosis: a consensus report. *Am J Clin Nutr* 1992; 55:108-116.
19. Kalnins D, et al, (abstr) *Ped Pulmonol* 1995; Supplement 12:266.
20. Hendeles L, Dorf A, Stecenko A, Weinberger M. Treatment failure after substitution of generic pancrelipase capsules. Correlation with *in vitro* lipase activity. *JAMA* 1990; 263:2459-2461.

21. Kraisinger M, Hochhaus G, Stecenko A, Bowser E and Hendeles L. Clinical pharmacology of pancreatic enzymes in patients with cystic fibrosis and *in vitro* performance of micro-encapsulated formulations. *J Clin Pharmacol* 1994;34:158-166.
22. Lifshitz F, Ament ME, Kleinman RE, et al. Role of juice carbohydrate malabsorption in chronic nonspecific diarrhea in children. *J Pediatr* 1992; 120:825-829.
23. Koocher GP, McGrath ML, Gudas LJ. Typologies of nonadherence in cystic fibrosis. *J Dev Behav Pediatr* 1990; 11:353-358.
24. Dutta SK, Hubbard VS, Appler M. Critical examination of therapeutic efficacy of a pH-sensitive enteric-coated pancreatic enzyme preparation in treatment of exocrine pancreatic insufficiency secondary to cystic fibrosis. *Dig Dis Sci* 1988; 33:1237-1244.
25. Durie PR, Bell L, Linton W, Corey ML, Forstner GG. Effect of cimetidine and sodium bicarbonate on pancreatic replacement therapy in cystic fibrosis. *Gut* 1980; 21:778-786.
26. Boyle BJ, Long, WB, Balistreri WF, Widzer SJ, Huang N. Effect of cimetidine and pancreatic enzymes on serum and fecal bile acids and fat absorption in cystic fibrosis. *Gastroenterology* 1980; 78:950-953.
27. Robinson P, Sly PD. Placebo-controlled trial of misoprostol in cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1990; 11:37-40.
28. Heijerman HG, Lamers CB, Bakker W. Omeprazole enhances the efficacy of pancreatin (pancrease) in cystic fibrosis. *Ann Intern Med* 1991; 114:200-201.
29. Zerlin JM, Kuhn-Fulton J, White SJ, et al. Colonic strictures in children with cystic fibrosis. *Radiology* 1995; 194:223-226.
30. Collins M, Azzarelli B, Stevens J, West K, Chong S, Fitzgerald J. Neural hyperplasia in colonic strictures (CS) of cystic fibrosis patients receiving high-dose pancreatic supplements. *Modern Path* 1995; 8:1P.
31. MacSweeney EJ, Oades PJ, Buchdahl R, Rosenthal M, Bush A. Relation of thickening of colon wall to pancreatic-enzyme treatment in cystic fibrosis. *Lancet* 1995; 345:752-756.