Pancreatic Enzyme Replacement Therapy use in infants with cystic fibrosis diagnosed by newborn screening

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Abstract

Objectives—To describe pancreatic enzyme practices during the first year of life in infants with cystic fibrosis (CF) and evaluate associations between dosing and outcomes, including growth and gastrointestinal symptoms.

Methods—We analyzed data from a subset of infants who were in a prospective cohort study conducted at 28 US CF centers. Anthropometric measurements and medications were recorded at each visit. Diaries with infant diet, pancreatic enzyme replacement therapy (PERT) dosing, stool

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frequency and consistency and pain were completed by a parent/guardian for three days prior to each visit.

Results—231 infants were enrolled in the main study; 205 of these met criteria for pancreatic insufficiency. PERT dose between birth and 6 months was on average 1882 LU/kg/meal (range: 492 – 3727) and was similar between 6 months and 12 months (mean: 1842 LU/kg/mean, range: 313 – 3612). PERT dose had a weak, negative association with weight z-score at 3 and 6 months (r = −0.16, 95% CI = −0.29, −0.02 and r= −0.18, 95% CI= −0.31, −0.04, respectively) but not at 12 months. There was not a clear relationship between PERT dosing and number of stools/day, stool consistency or pain. 144 infants (70%) were placed on acid suppression medication. Weight z-score mean was 0.37 higher in infants using proton pump inhibitors exclusively vs those using histamine-2 blockers exclusively (95% CI= −0.02, 0.76, p=0.06).

Conclusions—We did not observe that centers with a higher PERT dosing strategy yielded greater clinical benefit than dosing at the lower end of the recommended range.

Keywords

pancreatic enzyme replacement therapy; cystic fibrosis; growth; infancy

INTRODUCTION

Pancreatic enzyme replacement therapy (PERT) is essential for nutrient digestion and absorption required for growth and development in infants with cystic fibrosis (CF) and pancreatic insufficiency (PI), collectively known as CF-PI. Use of PERT has also been critical in preventing early or serious gastrointestinal (GI) complications of malabsorption, diarrhea and vitamin deficiencies in infants diagnosed with CF-PI. Despite the long history of PERT use in infants with CF, the doses used early in life and strategies to change doses are based on consensus recommendations. Those recommendations themselves are based on historical practices..[1–3] Most infants in the United States are now diagnosed with CF within the first few weeks of life[4,5] and those with PI are treated with PERT at an increasingly younger age[3]. CF centers across the US implement a wide range of PERT dosing when managing infants with CF to prevent malnutrition, however clear associations between PERT dose and growth in the first year of life are lacking.

The Baby Observational and Nutrition Study (BONUS) was a prospective multi-center study designed to assess growth, nutrition and other clinical outcomes in infants with CF during the first year of life. The primary aim of the study was to define and describe incremental weight gain and linear growth in the first year. As a potential significant modifier of growth, PERT dosing and adjustments based on clinical symptoms and growth parameters were recorded during the study period.

Despite the paucity of data to inform PERT dosing early in life, the underlying pathophysiology suggests that use of PERT is important for optimizing growth, development and overall health in infants with CF-PI. There is clearly a lower limit of efficacy, since lack of endogenous or exogenous (PERT) enzymes leads to severe malnutrition and developmental delays.[6–8] Adverse effects have also been documented when exogenous

PERT dose is too high with development of fibrosing colonopathy.[9] We aimed to use the extensive data collected in BONUS to describe the current state of PERT dosing in CF infants and investigate associations of PERT dosing with growth, feeding type, acid suppression medications and other clinical outcomes. We hypothesized that growth parameters and clinical outcomes are associated with PERT dose.

METHODS

Patients and Study Design

The Baby Observational and Nutrition Study (BONUS) was a prospective cohort study of infants with CF enrolled from birth to 3.5 months of age conducted at 28 US CF centers.[10] In brief, exclusion criteria were: <35 weeks gestational age, birth weight < 2.5 kg, or inability to take full oral feeds. Concomitant medications were recorded at each visit, including but not limited to PERT dose and use of acid-suppressing medications. Anthropometric measurements were performed by study certified staff.[11] Diaries were completed by a parent/guardian for three days prior to each scheduled clinic visit to collect information regarding infant diet, PERT dosing, meal frequency, stool frequency, stool consistency using the modified pediatric Bristol Stool Form Scale (mpBristol)[12] and pain (modified pain diary)[13]. ESHA Research software was used for nutritional analysis (Salem OR, USA). Participating parent/guardian provided written informed consent and all sites received Institutional Review Board approval (ClinicalTrials.gov NCT01424696).

Definitions and Statistics

World Health Organization (WHO) standard growth curves [14,15] were used to calculate attained weight, length, and occipital-frontal circumference (OFC) for age z-scores. Babies were classified as PI if they had a fecal elastase (FE) result 200 μg/g or if they had two PI causing CFTR mutations.[16] If this information was unavailable, PERT use at study termination was used as a surrogate; all infants who were prescribed PERT are included in these analyses. PERT dose at each visit was calculated as lipase units (LU)/kg/meal, LU/kg/day[17]. For exclusively formula fed infants, LU/g fat/day was calculated using the average daily fat intake (g) over the 3 day diet diary associated with that visit. PERT dose was summarized using maximum dose by 6 months of age and between 6 and 12 months of age and stratifying into three categories: <1000, 1000–2000, and 2000 LU/kg/meal. The frequency and timing of PERT dose adjustments were also calculated per patient. Dose adjustments were categorized as maintenance (± <300 LU/kg/meal), increase or decrease (± 300 LU/kg/meal). Rates of dose change were calculated accounting for follow-up time.

As this was an observational study, treating clinicians were free to determine and adjust PERT dose based on their usual clinical practice within their institutions. A post hoc clustered site analysis to compare sites dosing infants with a lower PERT dose (85% of patients at site with a median dose<1500 LU/kg/meal) vs. a higher PERT dose (85% of patients at site with a median dose 1750 LU/kg/meal) was utilized to explore associations between PERT dose and clinical outcomes (weight, length, GI symptoms). Additionally, associations between PERT dosing and GI symptoms, feeding type (breast feeding, formula, or both), CFTR genotype class, meconium ileus, and acid suppressing medications

(histamine-2antagonists/blockers [H2 blockers] and proton pump inhibitors [PPI]) were explored.

Summary statistics including means, medians, standard deviations [SD], ranges, and 95% confidence intervals (CI) are reported. Differences and comparisons are made with one and two-sample t-tests, Fisher's exact test for categorical data, ANOVA, Mann-Whiney test, or Pearson's correlation coefficient; 95% CIs were calculated and all p-values were two-sided. (SAS V9.4, R V 3.16.)

RESULTS

Cohort Description

Between 2011 and 2014, 231 infants were enrolled in BONUS [10]. Of the 231 enrolled BONUS babies, 210 (91.0%) initiated PERT and 205 (97.6%) of those were PI by study definition or were taking PERT; 25 (12.2%) were diagnosed with meconium ileus (MI). Of the 205 babies initiating PERT, 182 (88.8%) had a fecal elastase result 200 μg/g, 186 (90.7%) had two class I–III CFTR mutations (126 homozygous F508del), 10 (4.9%) had at least 1 class IV–V mutation, 8 (3.9%) had one class I–III and an unreported/unidentified mutation, and 1 (0.5%) had two unknown/unidentified mutations (Table 1).

PERT Use and Dosing

In this cohort, PERT was always initiated before 5 months of age with a mean age of 2.0 months (range: 0.0 – 4.3). Two PERT brands were predominant (>95%), with remainder shared among two other brands. Ten percent of babies switched brands at least once in the first year of life. Each participants' maximum PERT dose between birth and 6 months was on average 1882 LU/kg/meal (range: 492 – 3727) and was 12259 LU/kg/day (range: 2358–28139). The dose per meal was similar between 6 months and 12 months (mean: 1842 LU/kg/meal, range: 313 – 3612; the mean daily dose was somewhat lower (10689 LU/kg/day, range: 1660–26388). On average babies ate 6.3 times/day at 3 months (range: 3–12), 5.9 times/day at 6 months (range: 1–12), and 5.5 times/day at 12 months (range: 3–12). The majority of participants were treated with a PERT dose exceeding 2000 LU/kg/meal (55%), while 5% were dosed with less than 1000 LU/kg/meal (Table 1). Maximum PERT dose over the first year of life was similar across genotype classes and breast-feeding status (see online Figure, Supplemental Digital Content 1). Among exclusively formula fed babies, average maximum PERT dose was 2815 (SD=2254) LU/g fat/day (range: 421–12459) in the first 6 months (n=134), and 2941 (SD=1997) LU/g fat/day (range: 384–12422) between 6 and 12 months of age (n=155).

PERT dose and association with Weight and GI Symptoms

PERT dose (LU/kg/meal) had a weak, negative association with weight z-score at 3 and 6 months (r = −0.16, 95% CI = −0.29, −0.02 and r= −0.18, 95% CI= −0.31, −0.04, respectively) but not at 12 months (Figure 1a–c). The average 6-month weight z-scores were slightly lower in those receiving the higher range of PERT dosages during the year (>2000 LU/kg/meal 6 month weight z= −0.64 compared to z= −0.44 for 1000–2000 LU/kg/meal and z= −0.26 for <1000 LU/kg/mean, p=0.26). A similar trend was seen for 12-month weight z-

scores (>2000 LU/kg/meal 12 month weight z= −0.17 compared to z= 0.03 for 1000–2000 LU/kg/meal and z= 0.13 for <1000 LU/kg/mean, p=0.27). PERT dosage was not associated with the number of stools reported per day at 6 months (p=.60) or 12 months of age (p=0.75). Stool consistency as reported by the mpBristol (range: 1="separate hard lumps", 5="watery, no solid pieces") was mean (SD): 4.04 (0.78) 3 months, 3.81 (0.72) at 6 months, and 3.36 (0.96) at 12 months. Overall reported pain was low (mean <1 on scale from 0–10 where 0= no pain), and pain at 12 months was similar among the babies with lower versus higher maximum PERT dose (>2000 LU/kg/meal average pain score= 0.35 compared to 0.51 for 1000–2000 LU/kg/meal and 0.60 for <1000 LU/kg/mean, p=0.46).

Of the 478 recorded PERT dose changes during the study interval up to 12 months of age, 58% (n=276) were classified as maintenance (dose change± <300 LU/kg/meal) whereas 34% (n=164) were classified as dose increases and 8% (n=38) as dose decreases. On average, babies had 1.88 maintenance dose changes, 1.4 dose increases and 1.09 dose decreases during the follow-up period. Thirty-six percent (74/205) did not have any dose change; 117 (57%) had at least one dose increase and 35 (17%) had at least one dose decrease while 21 (10%) had both. More frequent dose changes were associated with lower weight (r= −0.17 p=0.02 at 6 months and r= −0.22, p=0.003 at 12 months) and less weight gain between 3 and 12 months (−0.64 weight z-score units per active dose change, 95% CI −1.1, −0.2; p=0.006). There were no clear associations between active dose changes and pain or number of stools.

Use of Acid Suppression

Of the 205 PI infants in the BONUS cohort, 144 (70%) were placed on acid suppression medication at some time during the first year of life; over half (77/144) started acid suppression before enrolling into BONUS (mean age of enrollment 2.6 months[10]). Sixty-three (30.7%) were exclusively on H2 blockers, 34 (16.6%) received only PPIs, and 47 received both (22.9%). Among those who received both, 83% initiated H2 blockers on average 1 month before PPI. Overall, babies were on H2 blockers for an average of 26 weeks (n=110, SD=15.3), and PPIs for an average of 31 weeks (n=81, SD=14.1). Half of babies only using PPIs had a twelve-month weight-for-age z-score >0, whereas 36.5% of babies using exclusively H2 blockers achieved weight-for-age z-score >0 at 12 months (see Table, Supplemental Digital Content 3) (z-score mean 0.37 higher in PPI vs H2 only, 95% CI= −0.02, 0.76, p=0.06). Babies on both H2 blockers and PPI did not have improved weight at 12 months compared to those on H2 blockers alone (mean z-score difference: −0.03, 95% CI= −0.41, 0.35, p=0.86). Fewer babies on PPI had a maximum dose > 2000 LU/kg/meal at 6 and 12 months than those on H2 blockers only (see Table, Supplemental Digital Content 3).

Higher dosing sites versus lower dosing sites

PERT dosing practices varied by site. Five sites (n=43) met the definition of higher PERT dosing (85% of participants' median PERT dose was 1750 LU/kg/meal), while 5 sites (n=36) were dosing PERT in a lower range (85% of participants' median PERT dose was <1500 LU/kg/meal) (Figure 2). All others were classified as mid-range. Site characteristics are shown online (see Table, Supplemental Digital Content 4). Gender, genotype

distribution, breast feeding, birth weight, incidence of meconium ileus, and preference for PERT brand were similar. Use of proton pump inhibitors alone was more common at lower dosing and mid-range dosing sites, although no acid blocker use, use of H2 blockers alone and the combination of H2 blockers and PPIs was similar across all sites.

Weight for age z-score did not differ significantly by lower versus higher PERT dosing (p=0.41, Figure 3a) at 12 months where average in the lower dosing sites was −0.03 (95% CI= −0.32, 0.27) compared to 0.01 (95% CI = −0.22, 0.25) in the higher dosing sites. Average weight for age z-score at the mid-range site was −0.11 (95% CI= −0.29, 0.07). There were no overall differences in length for age z-score by lower versus higher dosing strategy (p=0.095, Figure 3b). The 12 month length-for age z-score in the lower dosing sites was −0.82 (95% CI= −1.13, −0.51) compared to −0.45 (95%CI= −0.78, −0.12) in the higher dosing sites, and −0.65 (95% CI= −0.83, −0.47) in the mid-range dosing sites.

There was not a clear relationship between PERT dosing and GI symptoms. The distribution of stool consistency (mpBristol) did not differ across lower dosing and higher dosing sites at either 6 or 12 months (p = 0.33, p = 0.70). At 3 months, there was a trend toward watery stools (mpBristol type = 5) in the babies at lower dosing sites (33.3%) vs higher (11.6%; p = 0.03). There was more laxative use at the lower dosing sites. Serum alpha-tocopherol levels were higher in the higher dosing sites at 6 months but were within the normal range at lower dosing sites; that difference was attenuated at 12 months (see Table, Supplemental Digital Content 4).

DISCUSSION

The data from this prospective, observational study indicate that clinicians prescribe a wide range of PERT doses to infants in the first year of life. Mean dose per meal was in the higher mid-range. The slightly higher total daily dose in the first six months of life likely is consistent with the increased number of feedings during this early time of life[17]. Despite longstanding practice and consensus recommendations to "optimize" PERT dosing[18], we did not observe a dose-response effect on weight gain or height in this large cohort of infants assessed at 3, 6 and 12 months of life. Although the average 6-month weight z-scores were lowest in those receiving higher PERT dosages, this likely represents indication bias rather than cause and effect as practitioners may perceive that weight is faltering due to reduced fat absorption, leading them to increase PERT dose. One might also consider a similar clinical bias at the lower end of the dosing range as well – that is, these infants are growing well and thus the dose was not increased. Using differences in practice patterns by site, we were able to conduct a natural experiment comparing PERT dosing strategies on weight gain and linear growth. In this setting, where indication bias is presumably diminished, weight and length for age z-score did not differ significantly between sites that dosed PERT at the lower end of the recommended range versus those who tended to dose at the higher end, therefore strengthening our observation of lack of effect of PERT dose on growth in BONUS infants.

CF clinicians have been trained to increase PERT dose in response to frequent or loose stools and have worried that higher doses of PERT can cause constipation or lead to fibrosing colonopathy. Based on parent/guardian diaries, PERT dosage and change was not

associated with number of stools per day. Although there appears to be some trends toward softer stool consistency (mpBristol) at the lower dosing sites at 3 months, the differences go away by 6 and 12 months. Of note, lower dosing sites tended to use more laxatives. This study did not collect information on the rationale for use of laxatives; no correlation was seen between stool consistency and laxative use. There are no specific recommendations about the use of laxatives in infants with CF[3]. The amount of pain reported and the odds of more intense pain tended to be less among the babies with higher maximum PERT dose; however, our pain scale was not specific to abdominal pain. As with the number of stools, there was no clear association between active dose changes and pain scores.

Delayed buffering of gastric pH has been observed in adults with CF[19] and a higher luminal pH (>5.5) is needed for optimal dissolution of enteric coating of PERT[1,20]. In addition, gastro-esophageal reflux may lead to feeding difficulties. Both of these theoretical rationales likely contributed to the 70% use of any acid blockade in these infants with CF who are at risk for poor growth. This rate of acid blockade use is more than twice as high as that observed in a cohort of premature infants, although in that study these medicines were likely used exclusively for treatment of GER[21]. We have previously shown that use of H2 blockers, either alone or in combination with a PPI, are associated with increased risk of lower weight or length in this cohort [10]. In this further analysis, we observed that at one year of age, half of babies using PPIs exclusively had a weight-for-age z-score above the mean for the healthy population versus 36% of those on H2 blocker alone. PPIs act by irreversibly blocking the hydrogen-potassium adenosine triphosphatase enzyme system (H^+/K^+ ATPase) of gastric parietal cells as well as other cells that generate hydrogen potassium gradient. Complications in bone health as well as other immune mediated dysregulation has been linked to the changes induced by PPI[22]. H2 receptors are present in parietal cells and when blocked, gastric acid secretion is minimized. However, H2 receptors are also present in other tissues and hematopoetic cells. H2 blockers may suppress IL-12 and stimulate IL-10 production[23]. Decreased production of IL-10 in CF bronchi has been suggested as a mechanism that contributes to increased local inflammation and tissue damage[24]. One might speculate that non-acid-blocking effects of H2 blockers could be a factor in suboptimal growth. Nonetheless, our observations indicate that more guidance is needed if acid suppression therapy is used in infants with CF.

An observational study cannot prove cause and effect; however we have not identified any clear associations between PERT dose with infant weight gain and GI symptoms. By coincidence, sites self-segregated based on their PERT dosing, giving us a post-hoc opportunity to examine and confirm the relationship between higher and lower PERT and outcomes without the confounding effect of indication bias. This designed allowed us to look for a PERT dose effect and did not observe one; however almost all CF infants were dosed within the recommended range, therefore there may be threshold for PERT efficacy at the lower end of that range. A dose escalation study would determine whether a dose plateau exists with PERT use. Use of H2 blockers or PPI for acid blockade may have been influenced by clinician practice or by payor preference. The use of both H2 blockers and PPI in combination may indicate a suboptimal "step up" strategy; our observations suggest that there is no clinical benefit to this approach.

Although our findings are contrary to standard PERT recommendations in infants, they represent the best evidence to date concerning PERT dosing and clinically relevant endpoints. Improved growth early in life is associated with better clinical outcomes later in life[25], thus if an optimal infant dose of PERT could be determined it would be an important therapeutic recommendation. A recent review of older individuals in the US Cystic Fibrosis Patient Registry indicated that a somewhat higher mid-range dose of PERT was associated with better growth and BMI than a lower mid-range dose.[26] The mean dose of PERT used in this cohort was in the higher mid-range and the majority of infants with PI enrolled in a BONUS study grew well[10]; however we did not observe that a higher PERT dosing strategy yielded greater benefit than dosing at the lower end of the recommended range.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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What is known

- Cystic fibrosis (CF) causes pancreatic insufficiency and complications early in life.

- Use of pancreatic enzyme replacement therapy (PERT) is common in CF but optimal dosing and how it relates to infant growth is unknown.

- Use of acid suppression is common in infants with CF although clinical correlates have not been well-defined.

What is new

- Infants with CF who are pancreatic insufficient receive a wide range of PERT dosing across US institutions.

- In this observational study, there is no association between PERT dosing and growth parameters.

- Use of acid suppressing medication was common in this cohort and there was an association with better weight z-score at 12 months with proton pump inhibitor (PPI) use compared to histamine-2 blockers.
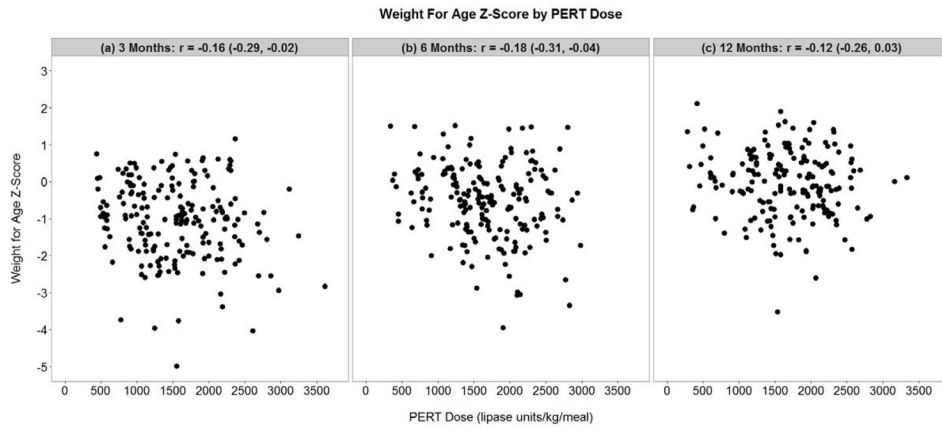
Figure 1.
Weight for age z-score by PERT dose at (a) 3, (b) 6, and (c) 12 months.
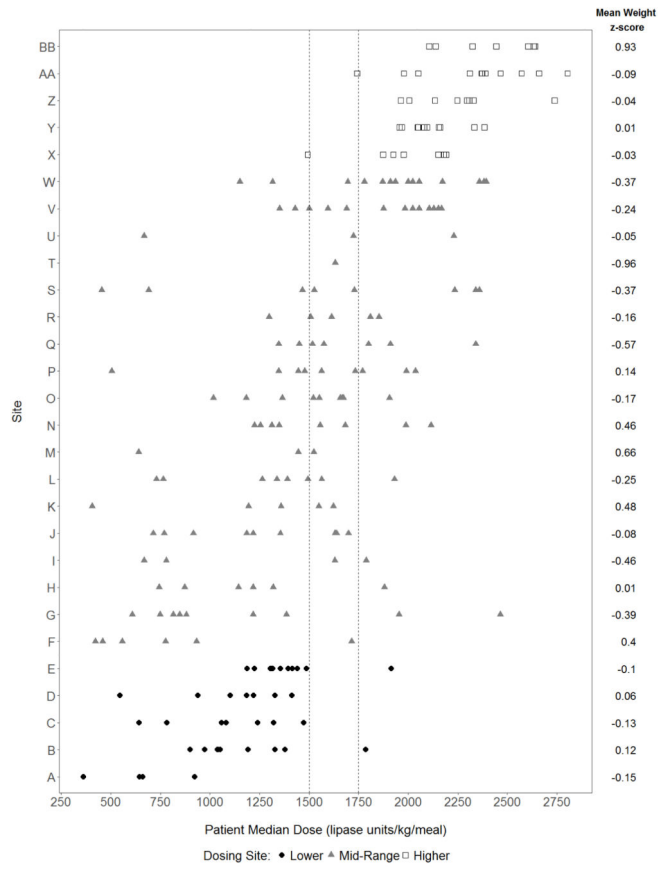
Figure 2.
Participant median dose (over entire year) and mean 12 month weight for age z-score by
Site. White squares= higher dosing sites' participants; black circles=lower dosing sites'
participants; gray triangles=mid-range dosing sites' participants
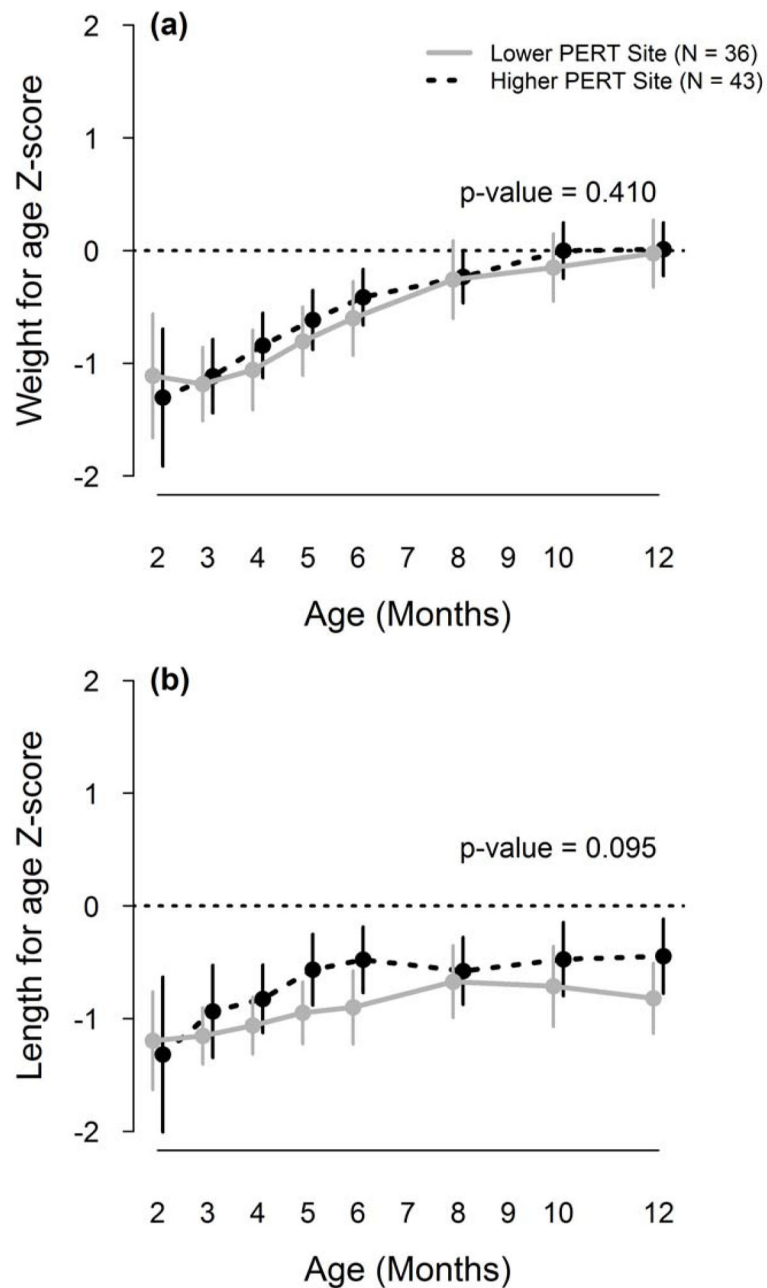
Figure 3.
Average weight and length for age over the first year of life by site PERT dosing. Gray solid line= lower PERT dosing sites; black hashed line= higher PERT dosing sites; p-value is for overall test of difference between curves.

Table 1

Cohort Characteristics by pancreatic status and PERT use among those with PI

	BONUS CF infant Cohort N = 231		
	PI + initiated PERT N = 205	PI + no PERT use N = 6	PS N = 20
Fecal Elastase (µg/g)			
50	144 (70.2%)	1 (16.7%)	0 (0%)
50– 100	25 (12.2%)	0 (0%)	0 (0%)
100– 200	13 (6.3%)	1 (16.7%)	0 (0%)
>200	1 (0.5%)	2 (33.3%)	16 (80%)
Unavailable	22 (10.7%)	2 (33.3%)	4 (20%)
Genotype Class			
I–III/I–III	186 (90.7%)	6 (100%)	3 (15%)
IV–V/any	10 (4.9%)	0 (0%)	9 (45%)
I–III/unknown	8 (3.9%)	0 (0%)	8 (40%)
Unknown/unknown	1 (0.5%)	0 (0%)	0 (0%)
Meconium Ileus			
Yes	25 (12.2%)	1 (16.7%)	1 (5%)
No	180 (87.8%)	5 (83.3%)	19 (95%)
Birth weight z-score (mean, SD)	–0.19 (0.88)	0.26 (1.17)	0.08 (1.09)
Breastfeeding Status			
Excl BF at 3 mos	54 (26.3%)	2 (33.3%)	1 (5%)
BF and FML @ 3 mos	38 (18.5%)	0 (0%)	6 (30%)
Excl FML @ 3 mos	112 (54.6%)	3 (50.0%)	12 (60%)
Acid Blocker Usage			
None	61 (29.8%)	5 (83.3%)	12 (60%)
PPI only	34 (16.6%)	0 (0%)	3 (15%)
H2 Blocker only	63 (30.7%)	0 (0%)	5 (25%)
PPI + H2	47 (22.9%)	1 (16.7%)	0 (0%)
Participant specific max PERT dose 0–6 mos			
Lipase Units/Kg/Meal			
N	205		
mean (sd)	1882 (621)		
min, max	492, 3727		
<1000	18 (8.8%)		
1000–2000	99 (48.3%)		
>2000	88 (42.9%)		
Participant specific max PERT dose 6–12 mos			

	BONUS CF infant Cohort N = 231		
	PI + initiated PERT N = 205	PI + no PERT use N = 6	PS N = 20
Lipase Units/Kg/Meal			
N	196		
mean (sd)	1842 (617)		
min, max	313, 3612		
<1000	20 (9.8%)		
1000–2000	90 (43.9%)		
>2000	86 (42.0%)		

PI=pancreatic insufficient; PS= pancreatic sufficient; SD=standard deviation; Excl= exclusive; BF=breast fed; FML=formula fed; PPI=proton pump inhibitor