

Evaluation of a free amino acid–based formula in infants with presumptive food protein–induced proctocolitis

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Abstract

Objective: Food protein–induced proctocolitis usually occurs early in life and is characterized by blood-streaked stools and pain during defecation in an otherwise healthy infant. While many infants with food protein–induced proctocolitis respond well to a casein hydrolysate formula, some require an amino acid–based formula. The objective of the study was to measure the change in physician-rated symptom score from enrollment to study completion in infants with presumptive food protein–induced proctocolitis fed with a specific amino acid-based formula.

Methods: In this study, infants ≤ 6 months of age diagnosed with presumptive food protein–induced proctocolitis received an amino acid-based formula for 42 days. Intake, stool patterns, weight, stool occult blood, and questionnaires assessing infant feeding and stool patterns and parental formula satisfaction were collected.

Results: The full analysis set included 43 infants. The mean age at enrollment was 59 ± 5 days. A significant improvement was observed from enrollment to exit in physician-rated symptom score (9.1 ± 0.5 to 4.8 ± 0.5 , $p < 0.0001$), the number of infants with occult blood in stool, and weight-for-age Z-scores during the study. Parental satisfaction with the formula was high.

Conclusion: The results confirm that the amino acid-based formula studied is efficacious for managing symptoms of presumptive food protein–induced proctocolitis.

Keywords

Amino acid–based formula, elemental formula, food protein–induced proctocolitis, eosinophilic proctocolitis, hypoallergenic formula, infant, infant formula

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Introduction

Many types of gastrointestinal reactions to foods can occur in infants. Regardless of the mechanism, many of the symptoms associated with the reactions are similar, but vary in time of onset, severity, and persistence. Food protein–induced proctocolitis (FPIP), first described in breastfed infants, usually occurs during the first few months of life in response to cow milk or soy protein and is characterized by blood-streaked stools in an otherwise well infant.¹ Endoscopic evaluation of the rectosigmoid region frequently displays focal erythema and friability.¹ Morita et al.² have recently described common findings of lymphonodular hyperplasia with an oozing and edematous mucosal surface. Lake¹ has reported that histopathological findings from the rectosigmoid region of these infants are markedly consistent with striking eosinophilic infiltration of the colonic epithelium, lamina propria, and even the muscularis. The finding

of a specific number of eosinophils/high-power field (HPF) has been proposed to be of use in diagnosis of FPIP, however, as of yet there is no agreed upon criteria.³ Lake has

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stated that the number of eosinophils varies from 6 to more than 20 eosinophils/HPF and has proposed 20 eosinophils/HPF as a possible threshold.^{1,4} Most authors have used 20 eosinophils/HPF.³

The standard treatment of FPIP is elimination of the suspected food protein.² A hypoallergenic extensively hydrolyzed formula (EHF) or an amino acid–based formula (AAF) is typically recommended for formula-fed infants with suspected FPIP.^{1,2,4–6} While most infants respond well to an EHF, some may require an AAF^{1,4–7} if symptoms persist on a EHF. With restriction of the offending protein(s), infants typically tolerate an unrestricted diet after 9 months of age.¹ In actuality, the vast number of such infants will be seen by their primary care provider, receive a dietary change, and never receive conclusive confirmation of the diagnosis because the symptoms responded to dietary change. Dietary restriction of the protein(s) of concern will alleviate gross bleeding within approximately 72–96 h.^{1,5} Most of these infants will continue to be managed by their primary care providers who will refer infants to a specialist only after an infant has failed to improve following dietary change.⁸

Despite recommendations for the use of AAF to treat some infants with FPIP, there is a paucity of data regarding its use in infants with this condition. In order to generate efficacy data for infants with presumptive FPIP fed with a specific AAF, we conducted a prospective study to evaluate FPIP-related symptoms, growth, and formula tolerance in infants who were fed a specific AAF for 42 days.

Methods

Study design

This was a one-group, suitability study (ClinicalTrials.gov Identifier NCT01813526) conducted in infants 0–6 months of age with presumptive FPIP. The primary objective was to measure the change in physician-rated symptom scores (PRSSs) from enrollment to study completion. The PRSS assessment was developed by the investigators prior to the study and was based on their clinical experience with infants with FPIP. Changes in weight, World Health Organization (WHO) weight-for-age Z-scores, the number of infants with occult blood in stools, stooling patterns, and formula intake were also measured.

Subjects

Eligible infants met the following inclusion criteria: age \leq 6 months, 36–42 weeks gestational age at birth, negative stool cultures at study entry, were formula-fed at the time of study entry, had no prior history of having been fed an AAF, were diagnosed with FPIP by rectal or colonic biopsy at study entry or continued to be symptomatic on a casein-based EHF following a diagnostic rectal or colonic biopsy within 21 days of enrollment. Histological confirmation of

increased eosinophils in the lamina propria, eosinophils in the muscularis mucosa, eosinophils in crypt or surface epithelium, eosinophilic crypt abscess, or eosinophils in clusters was required for the diagnosis of FPIP. Exclusion criteria included maternal history of tuberculosis, intrauterine infections, suspected substance abuse, or other maternal conditions that investigators thought could have potential adverse effects on infant growth and/or development, and infant history of conditions other than FPIP considered by the study investigators to have potential negative effects on growth or development.

Parents were instructed to feed the formula ad libitum. Water was allowed, but not other formulas. Consumption of milk or soy products during the study was not allowed. Iron or fluoride supplements were allowed if prescribed by the infant's physician. Parents agreed not to administer products that could influence assessment of formula tolerance including herbal preparations, home remedies, over-the-counter medications, or corn syrup. The use of cisapride or systemic corticosteroids was not allowed, and was a reason for removal from the study.

Parents or guardians provided written informed consent prior to enrollment. Infants were recruited from pediatric gastroenterology clinics at two sites: Children's Hospital and Medical Center, Omaha, NE, USA, and Johns Hopkins Hospital, Baltimore, MD, USA. The study protocol was approved by the Institutional Review Board at each site, and was conducted in accordance with all applicable regulations, including Good Clinical Practices and the ethical principles originating from the Declaration of Helsinki.

Study formula

The study formula was EleCare[®] Amino Acid-Based Medical Food (Abbott Nutrition, Abbott Laboratories, Columbus, OH, USA) designed to provide 20 kcal/fl oz when fed at standard dilution. The formula was packaged in clinically labeled cases identified only by clinical product number and provided levels of nutrients recommended by the American Academy of Pediatrics Committee on Nutrition, as regulated by the Infant Formula Act⁹ and all subsequent amendments.¹⁰

Study assessments

Infants were seen at study visits on study days (SD) 1 and 43. Parents began feeding the study formula at the first feeding after enrollment, and fed the formula for the duration of the study. Telephone assessments were made by study staff on approximately SD2, and on SD15 and SD36. On SD1, infants were weighed and the study physician conducted a PRSS assessment documenting FPIP-related symptoms displayed by the infant. The PRSS assessment included assessment of symptoms of FPIP such as blood in the stool, difficulty passing stool (pain with defecation), eczema, diarrhea (stool frequency, diaper rash) noted by Lake¹ to be observed in

breastfed infants with the condition as well as assessments of irritability, vomiting, spit-up, sleep problems, and reactive airway disease. At the SD43 visit, a second PRSS assessment was completed. Parents completed formula intake and stool records for two time periods: from the first study formula feeding on SD1 through the subsequent three days and for three days prior to SD43. The records included the characteristics (consistency and frequency) of the infant's stools, volume of study formula consumed at each feeding, consumption of foods other than the study formula, and incidences of spit-up and vomiting. Mean rank stool consistency (MRSC) of infant stools was calculated using a 5-point scale (1=watery, 2=loose, mushy, 3=soft, 4=formed, 5=hard). Hemocult cards[®] (Hemocult SENSE; SmithKline Diagnostics, Inc., San Jose, CA, USA) were used to detect the presence of fecal blood. On SD1, parents were instructed how to collect stool for determination of occult blood and were given a sufficient quantity of Hemocult[®] cards to prepare from the infant stools on SD2–4 and SD40–42. At least one stool was to be tested on each of the designated days. Parents completed an Infant Feeding and Stool Patterns Questionnaire and a Formula Satisfaction Questionnaire at the SD43 visit.

Statistical analyses

A sample size of 30 infants was estimated to have 80% power to detect a difference in means of 0.529 standard deviations in PRSS using a paired t-test with a 0.05 significance level. Although no previous data on PRSS were available for calculation of sample size, a sample size of 30 is generally large enough for large sample approximations (the Central Limit Theorem) to hold.¹¹

A paired t-test was used to analyze the changes from SD1 to SD43 in PRSS, MRSC, formula intake, weight, and the weight Z-score. The Wilcoxon signed-rank test was used to analyze changes in daily number of stools and to confirm the parametric results for PRSS since the distributions were skewed. Tests were carried out using SAS[®] procedure PROC UNIVARIATE. The change in occult blood status (positive to negative, and vice versa) from SD1 to SD43 was made using McNemar's test. The primary analysis was on the full analysis set (FAS), while another set of analyses was made on the subset of protocol evaluable (PE) infants, which included infants who completed the study and who did not receive over-the-counter medications, home remedies, or vitamin or mineral supplements for >15 days. Results were considered significant at the 5% level, and all tests were two sided. The study results are shown as the mean \pm the standard error of the mean (SEM), or the median and first to third quartile (Q1, Q3), and are for the FAS group unless otherwise noted.

Results

A total of 53 infants were enrolled and comprised the intent-to-treat (ITT) group (Figure 1); no infants were lost to

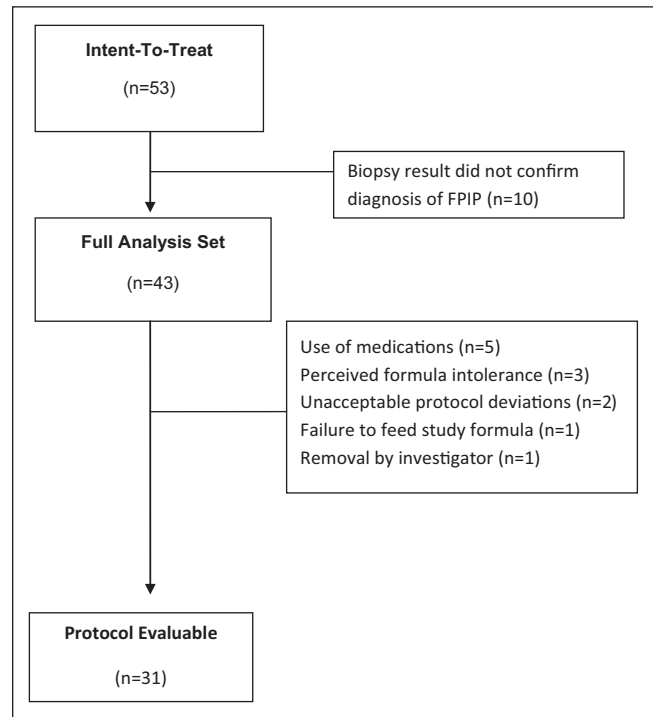


Figure 1. Disposition of study subjects.

FPIP: food protein–induced proctocolitis; n: number.

follow-up. Of these, 10 infants were removed from the study when biopsy results were unable to confirm a diagnosis of eosinophilic proctocolitis; therefore, 43 infants with biopsy-confirmed eosinophilic proctocolitis and presumptive FPIP comprised the FAS group. A total of 12 infants in the FAS group were excluded from the PE group: 5 due to the use of medications, 3 due to perceived formula intolerance, 2 due to unacceptable protocol variations, 1 due to failure to feed the formula according to the protocol, and 1 due to removal by the investigator for reasons not related to the study formula, yielding 31 infants in the PE group. Of the three subjects who exited due to formula intolerance symptoms, one experienced vomiting and spit-up and was changed to another AAF (Neocate[®]; Nutricia North America, Rockville, MD, USA), but the symptoms persisted and Neocate feeding was also discontinued. One infant refused to drink the formula after 14 days and was changed to an EHF on which symptoms worsened and subsequently was changed to Neocate. On Neocate, the infant had complaints of constipation. The last infant was fussy and irritable after 28 days on study formula and was changed to Neocate with no improvement of symptoms. The mean age at enrollment was 59 ± 5 days and the mean birth weight was 3357 ± 77 g. Males comprised 51% of the FAS group. No safety concerns emerged during the study.

Biopsies were conducted at a mean of 1.9 ± 0.6 days (range 0–21 days) prior to enrollment. The proctosigmoidoscopy results for the FAS group revealed that 53%

Table 1. Changes in physician-rated symptom scores, weight-for-age Z-scores, stooling patterns, and formula intake for the FAS group from Study Day 1 to Study Day 43.

Characteristic	Study Day 1	Study Day 43	p value
Physician-rated symptom score ^{a,b,c} (n = 43)			
Vomiting	0.81 ± 0.16	0.30 ± 0.09	0.0079
Spit-up	1.65 ± 0.16	1.63 ± 0.16	0.9084
Irritability not associated with sleep	2.14 ± 0.16	0.93 ± 0.16	<0.0001
Stool frequency	0.77 ± 0.15	0.02 ± 0.02	<0.0001
Blood in stool	0.72 ± 0.14	0.09 ± 0.06	0.0002
Difficulty passing stool	0.88 ± 0.16	0.49 ± 0.11	0.0392
Sleep problems	1.35 ± 0.14	0.63 ± 0.16	0.0002
Diaper rash	0.40 ± 0.11	0.12 ± 0.06	0.0322
Eczema	0.37 ± 0.11	0.19 ± 0.08	0.1461
Reactive airway disease	0.00 ± 0.00	0.42 ± 0.16	0.0125
Total score	9.1 ± 0.5	4.8 ± 0.5	<0.0001
WHO weight-for-age Z-scores ^{c,d} (n = 37)	-0.62 ± 0.20	-0.10 ± 0.19	<0.0001
Daily number of stools ^e (n = 36)	1.7 (1.3, 2.8)	1.0 (0.7, 1.8)	<0.0001
MRSC ^{c,d,f} (n = 34)	2.5 ± 0.1	2.4 ± 0.2	NS
Formula intake, mL/kg/day ^{c,d} (n = 36)	151 ± 6	134 ± 6	0.0083

FAS: full analysis set; MRSC: mean rank stool consistency; NS: not significant; Q: quartile; SEM: standard error of the mean; WHO: World Health Organization.

^aBased on a 4-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe with specific criteria given for interpretation of each rating for each symptom, except reactive airway disease, which was scored as 0 = no, 3 = yes.

^bIncludes infants who exited from the study early.

^cMean ± SEM.

^dIncludes infants with data at both Study Day 1 and Study Day 43.

^eMedian (Q1, Q3).

^fMean rank stool consistency, scored as 1 = watery, 2 = loose/mushy, 3 = soft, 4 = formed, 5 = hard.

exhibited spontaneous friability, 82% exhibited erythema, and 50% exhibited both spontaneous friability and erythema. A median of 3 tissue samples (range 1–4) were collected from all FAS subjects for histological analysis of the rectosigmoid tissue. Analysis of the samples revealed increased eosinophils in the lamina propria (86% of infants), eosinophils in the epithelium (86% of infants), eosinophils in the muscularis mucosa (19% of infants), eosinophils in clusters (72% of infants), and eosinophilic crypt abscess (7% of infants).

The mean total PRSS for the FAS group decreased from 9.1 ± 0.5 on SD1 to 4.8 ± 0.5 on SD43 ($p < 0.0001$) (Table 1); values for the PE group were 9.6 ± 0.6 (SD1) and 4.0 ± 0.6 (SD43) ($p < 0.0001$). The mean PRSS for each symptom decreased significantly during the study, with the exception of reactive airway disease, spit-up, and eczema (Table 1). Of the 43 FAS subjects, 33 had stools tested for occult blood at entrance and exit from the study. Of these 33 infants, 15 had at least one stool positive for occult blood at study entry and none had heme positive stools at SD43 ($p = 0.0003$). There were significant increases in weight-for-age Z-scores ($p < 0.0001$) during the study, and mean weight gain was 34.3 ± 1.9 g/day (Table 1). There was a significant decrease in the mean daily number of stools ($p < 0.0001$), but there was no significant change in MRSC (Table 1). There was a significant decrease in the mean volume of

formula consumed ($p = 0.0083$) (Table 1). Similar results for each of these variables were seen for the PE group.

Responses on the SD43 Infant Feeding and Stool Patterns Questionnaire indicated that infants tolerated the formula. Of the parents, 95% were satisfied with the formula (84% very satisfied/11% somewhat satisfied), 92% wanted to continue to use the formula (76% definitely/16% probably), and 95% thought their infant seemed to like the formula (82% very much/13% somewhat).

Discussion

Infants with presumptive FPIP who were fed this AAF for 43 days displayed a significant improvement in physician-rated symptom scores (PRSS) and a significant increase in WHO weight-for-age Z-scores. Of the parents, 84% reported that they were very satisfied with the formula.

FPIP and other gastrointestinal reactions to foods in infants are often due to a reaction to cow milk protein, and, less often, soy. Elimination of the causative food protein(s) from the diet is the primary treatment—either by eliminating it from the maternal diet for breastfed infants or by switching the infant to a different formula.^{1,5,6,12} EHF are most commonly used; however, allergic responses can still occur because these formulas may contain residual peptides that can elicit an allergic response in some infants.^{7,13–15} AAFs

are the preferred choice for infants with enterocolitis, severe allergy, or failure to thrive, and infants whose symptoms persist with the use of EHF.^{1,5–7,13,16,17}

Limitations of this study included that (1) infants with biopsy-confirmed eosinophilic proctocolitis were not orally challenged with intact milk protein to confirm that the symptoms were milk protein related and (2) because the use of EHF was not restricted prior to entry, infants may have started to improve when the study formula feeding was initiated.

Although the simple presence of eosinophils is not diagnostic for allergic disease, a majority of infants with such findings appear to respond to elimination diets and may subsequently be found to respond to oral challenges of common food protein including cow milk, egg, or soy. Xanthakos et al.¹⁸ reported that in four formula-fed infants with repeated biopsy results over a 3–9-week period indicative of eosinophilic proctocolitis, all infants had resolution of rectal bleeding and improved or normal histology with the feeding of a casein-based EHF or the same AAF as the current study formula. Two additional infants who improved with elimination diet presented with similar initial biopsy results but the parents refused follow-up biopsies to document improvement. Vanderhoof et al.⁷ changed 25 infants with biopsy-confirmed colitis from an EHF to an AAF for 2 weeks. All of the infants had resolution of their symptoms. When re-challenged with the EHF, 17 of the 25 infants had recurrence of their symptoms, leading the authors to conclude that some infants with formula protein-induced colitis require an AAF to resolve symptoms. In this study, there was also a significant improvement in PRSS as well as decrease in the number of infants with occult blood in stool after 43 days of feeding with the study formula. The improvement in PRSS and possibly occult blood may have been even more remarkable in this study if the use of casein-based EHF had been restricted prior to enrollment. However, current practice is that most primary care providers change the diet of these infants prior to referral to a pediatric gastroenterologist and restricting the prior use of EHF along with AAF prior to enrollment into the current study would have made recruitment very difficult. This study extends the findings of Vanderhoof et al.⁷ and Xanthakos et al.¹⁸ and confirms in a larger sample of infants that the AAF used in this study improves symptoms and supports short-term growth in infants with presumptive FPIP. Longer term growth of healthy term infants fed with this study formula has been reported in a larger group of exclusively formula-fed infants from birth to 4 months of age.¹⁹

Recommendations by an Expert Panel instituted after the completion of this study suggest that diagnosis of FPIP be made after resolution of symptoms when the causative food is eliminated from the diet and recurrence of symptoms following an oral food challenge.²⁰ Typical of current clinical practice where infants are managed by their primary care providers, infants enrolled in this study were not orally challenged to confirm food protein allergy after improvement of symptoms with the study formula.

In addition, the Expert Panel concluded that although a colonoscopy and biopsy is not necessary to make the diagnosis, they will reveal lesions in the large bowel consisting of mucosal edema with infiltration of eosinophils in the epithelium and lamina propria.²⁰ However, in practice, because biopsy procedures are invasive and expensive, infants who do see a gastroenterologist are not likely to be biopsied. Xanthakos et al.¹⁸ reported that in a survey of pediatric gastroenterologists in 2005, only 8% would confirm the diagnosis with biopsy before changing the diet. Thus, the diagnosis is usually presumptive; the condition is reportedly over-diagnosed.¹⁸ In clinical practice and in some studies, infants are inconsistently biopsied²¹ and infants are not always orally challenged soon after initial resolution of symptoms^{17,18,22–24} to confirm that the microscopic diagnosis was due to food protein allergy. With an elimination diet, most infants will be able to tolerate the allergenic protein by 9–12 months of life¹ and are often challenged at that time. A strength of our study was that all infants were confirmed by biopsy to have eosinophilic infiltration in the rectosigmoid region. Biopsy results revealed that 10 of the enrolled infants (19%) did not have biopsy results consistent with FPIP and were dropped from the FAS group. Lake⁸ has noted that in such subjects, even biopsies at three levels can fail to detect inflammatory features due to the focal nature of the condition.

In summary, our study confirms the efficacy of the AAF used for managing infants with biopsy-confirmed eosinophilic proctocolitis and presumptive FPIP. Infants with presumptive FPIP fed with the study formula for 42 days had significant improvements in symptoms often related to FPIP and weight-for-age Z-scores, demonstrating the efficacy of the study formula for treating infants with this condition. Based on the high likelihood of efficacy of EHF, and the lower cost and wider availability of EHF compared with AAF, an EHF appears to be the first choice for primary care providers in managing infants with presumptive FPIP. However, if symptoms are not resolved with an EHF, a trial with an AAF such as the formula in this study is safe and more efficacious than an EHF. Infants with symptoms not resolved by an AAF should be referred to a gastroenterologist for further evaluation and possible biopsy to rule out other diagnoses.

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Declaration of conflicting interest

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