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Supported by
more than
30 years of
scientific
research



NUTRICIA
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Contents

For Neocate products available in Canada, go to **Neocate.ca**

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This manuscript contains a selection of the scientific evidence behind Neocate. Since its launch in the 1980's Neocate has developed along with our increasing understanding of food allergies and other complex gastro-enteropathies. Its successful use in multiple conditions in infancy has led to the development of an age-adapted range to meet the needs of growing children (from infancy through childhood and beyond).

Neocate now consists of a family of hypoallergenic products for both infants and older children, including nutritionally complete formulas and a solid food for special medical purposes. Neocate products should be used under medical supervision.

Neocate products are indicated for use in the dietary management of cow milk allergy, multiple food allergies and related gastrointestinal and allergic conditions, including eosinophilic esophagitis, food protein-induced enterocolitis syndrome, short bowel syndrome, malabsorption and gastroesophageal reflux.

Nutricia North America supports the use of breast milk wherever possible.

Foreword

Providing scientific evidence is an essential element in demonstrating product efficacy and should form an integral part of disease management.

Since 1983, there has been exponential growth in our understanding of food allergy, including Cow Milk Allergy (CMA), which is the most common food allergy in children during the first years of life. Over the past three decades, investigators and healthcare professionals have built an ever expanding CMA knowledge base, which has changed the way we diagnose and manage the condition. This expansion of information has been aided in part by the availability of evidence on amino acid-based formula (AAF).

I first learned about Neocate in the early 1990's. At the time I was interested in the multifaceted symptoms and immunologic mechanisms of CMA, and the use of various hypoallergenic, protein-hydrolysate formula for its dietary management in infants and children. From my clinical experience and research, it was clear that these milk protein hydrolysates were not always

adequate to manage all forms of IgE- and non-IgE-mediated CMA, and I saw the need for a completely hypoallergenic formula to treat these infants and children.

This led to the organization of several US-based clinical studies. Since then, my research colleagues and I have published a number of papers on the safety and efficacy of amino acid-based formula in the management of various forms of CMA, as well as other food allergic disorders such as eosinophilic esophagitis, that frequently involve multiple food allergies.

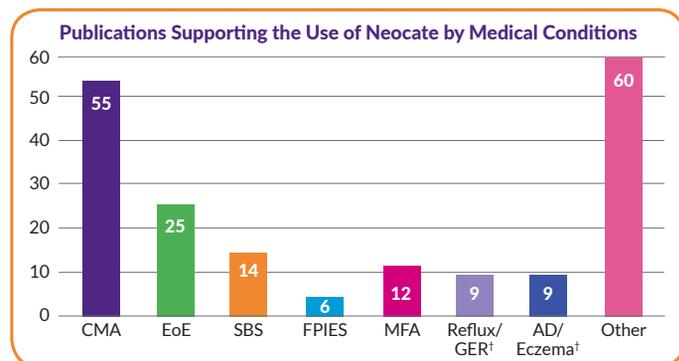
This document provides a summary of the extensive clinical research behind the brand Neocate, demonstrating its clinical efficacy through 30 years experience!

Hugh A Sampson, MD
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Over 175* publications and counting support the use of Neocate for a wide variety of conditions and ages

Neocate research has been presented worldwide at leading scientific meetings and published in major peer-reviewed journals

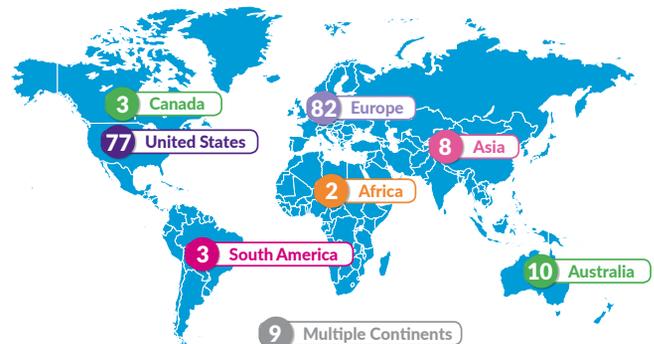
- NASPGHAN
- ASPEN
- Journal of Pediatrics
- Journal of Allergy and Clinical Immunology



*As of October 2018

FPIES = Food protein-induced enterocolitis syndrome; NASPGHAN = North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; ASPEN = American Society for Parenteral and Enteral Nutrition

†Conditions related to food allergies.



A world of confidence

- Neocate has been studied in children from 1 week to 18 years of age, and adults
- Evidence-based data
- 6 continents
- Year after year

Cow Milk Allergy (CMA) in Infants and Children

Publication	Title	Study Purpose	Methodology	Result/Conclusion	Page number
Infants					
Harvey BM et al. <i>Pediatr Res.</i> 2014;75:343-51	Effects on growth and tolerance and hypoallergenicity of an amino acid-based formula with synbiotics STUDY 1	To evaluate growth outcomes and formula tolerance in healthy infants fed Neocate with synbiotics.	Healthy infants (0-15 days) were randomly assigned to receive a control AAF or Neocate with synbiotics for 16 weeks. (n=115)	This study demonstrated that Neocate with synbiotics is safe, well tolerated and promotes normal growth when fed to healthy infants.	Abstract Page 5
	STUDY 2	To assess the hypoallergenicity of Neocate with synbiotics in IgE-mediated CMA.	Thirty infants & children with IgE-mediated CMA used Neocate with synbiotics followed by a DBPCFC. (n=30)	This study demonstrated that Neocate with synbiotics is safe, well-tolerated and hypoallergenic according to AAP guidelines.	Abstract Page 6
Burks AW et al. <i>Pediatr Allergy Immunol.</i> 2015;26:316-22.	Synbiotics-supplemented amino acid-based formula supports adequate growth in cow's milk allergic infants.	To evaluate growth outcomes and formula tolerance in infants with IgE- or non-IgE-mediated CMA fed Neocate with synbiotics.	Infants with CMA were randomly assigned to receive Neocate with synbiotics or a control formula (Neocate® Infant DHA/ARA) for 16 weeks. (n=110)	This study demonstrated that Neocate with synbiotics is safe and promotes normal growth in infants with CMA.	Abstract Page 7
Michaelis LJ et al. Oral abstract presented at EAACI Annual Meeting. Jun 11-15; Vienna, Austria. 2016. *Nutricia Advanced Medical Nutrition. Unpublished preliminary report on the primary outcome and safety findings of the ASSIGN trial. Data on file. 2016.	An amino acid-based formula with synbiotics affects faecal microbiota in non-IgE mediated cow's milk allergic infants.	To determine whether Neocate® Syneo® Infant will improve the developing gut microbiota in infant subjects with CMA relative to a standard AAF and healthy, breastfed infants.	Infants with non-IgE-mediated CMA were randomized to receive a control AAF or Neocate Syneo Infant for 8 weeks. A healthy breastfed reference group was also included.	This study demonstrated that Neocate Syneo Infant helps rebalance the gut microbiota of CMA infants, bringing it closer to that seen in age-matched, healthy breastfed infants*.	Abstract Page 8
Harvey BM et al. <i>J Pediatr Gastroenterol Nutr.</i> 2017;65:346-9.	Mineral intake and status of cow's milk allergic infants consuming an amino acid-based formula	To assess the mineral status of term infants diagnosed with CMA consuming an AAF for 16 weeks	Serum mineral levels were measured at baseline (n = 82) and after 16 weeks receiving an AAF, Neocate, with or without synbiotics (n = 66)	The AAF effectively supported adequate serum status of the selected minerals in CMA infants	Abstract Page 9
de Boissieu D et al. <i>J Pediatr.</i> 1997;131:744-7.	Allergy to extensively hydrolyzed cow milk proteins in infants: identification and treatment with an amino acid-based formula	To assess allergy to eHF in association with CMA	Infants with CMA who had been managed with eHF and still had persistent symptoms were initiated on an AAF (Neocate)	Feeding an AAF decreased symptoms within 3 days and improved weight gain	Abstract Page 10
Vanderhoof JA et al. <i>J Pediatr.</i> 1997;131:741-4.	Intolerance to protein hydrolyzed infant formulas: an under recognized cause of gastrointestinal symptoms in infants	To determine the effectiveness of an amino acid-based formula in infants with continued symptoms suggestive of intolerance of a casein hydrolyzed formula (CHF)	Infants who continued to have unresolved CMA-related gastrointestinal symptoms on CHF for an average of 40 days were switched to an AAF (Neocate)	Use of an AAF demonstrated resolution of CMA-related gastrointestinal symptoms within 14 days	Abstract Page 11
Infants and Children					
Berni Canani R et al. <i>J Pediatr Gastroenterol Nutr.</i> 2017;64:632-8.	Amino acid-based formula in cow's milk allergy: long-term effects on body growth and protein metabolism	To determine whether long-term use of an AAF can support adequate protein status and growth in CMA children	Infants with CMA were randomized to receive an AAF (Neocate) or eHF for 12 months, and compared to a healthy control group.	AAFs (Neocate infant and pediatric formulas) supported adequate protein status and normal growth	Abstract Page 12
Sampson HA et al. <i>Pediatrics.</i> 1992;90:463-5.	Safety of an amino acid-derived infant formula in children allergic to cow milk	To determine whether Neocate is safe for children with allergy to cow milk	Children with proven CMA used Neocate for 2 weeks followed by a challenge with an eHF	AAF (Neocate) proved to be hypoallergenic and well tolerated in children allergic to cow milk and may be slightly safer than eHF in children highly allergic to milk	Abstract Page 13

AAF = amino acid-based formula; ASSIGN = Amino acid-based formula with Synbiotics – Study in Infants with Gastrointestinal Non-IgE-mediated cow's milk allergy; CHF = casein hydrolyzed formula; CMA = cow milk allergy; DBPCFC = double-blind placebo-controlled food challenge; AAP = American Academy of Pediatrics; eHF = extensively hydrolyzed formula

Harvey BM, Langford JE, Harthoorn LF, et al. Effects on growth and tolerance and hypoallergenicity of an amino acid-based formula with synbiotics. *Pediatr Res.* 2014;75:343-51

STUDY 1

Background

This study was designed to examine the effects of an amino acid-based formula (AAF) with an added synbiotic blend on growth as well as tolerance in a group of healthy infants.

Methods

In a prospective, randomized, double-blind controlled study, healthy, full-term infants (n = 115) received either an AAF with an added synbiotic blend or an AAF that was already commercially available. Subjects received formula for 16 weeks. Primary outcome measures were growth, assessed by weight, length, and head circumference. Secondary outcome measures included gastrointestinal symptoms and stool characteristics. Also recorded were dietary intake, clinical laboratory results, and clinical examinations.

Results

There were comparable results between groups in the measured parameters of growth. Similar results between groups were also seen for tolerance. There were minimal differences seen between groups in stool characteristics and gastrointestinal symptoms through the course of the study.

Conclusion

This study showed that an AAF with an added synbiotic blend supports normal growth of healthy, full-term infants when fed as the sole source of nutrition. This study also demonstrates the safety and tolerance of an AAF with an added synbiotic blend with healthy, full-term infants.

Neocate with synbiotics and Neocate® Infant DHA/ARA* were both demonstrated to support normal growth.

An amino acid-based formula with prebiotics and probiotics, Neocate® Syneo® Infant is a nutritionally complete formula that is backed by this clinical trial in healthy infants to support normal growth and development and to be safe and well tolerated.

Translated and adapted from publicly available abstract - full English text available at <http://www.nature.com/pr/journal/v75/n2/full/pr2013211a.html>

* Known in Canada as Neocate® DHA & ARA infant formula

Harvey BM, Langford JE, Harthoorn LF, et al. Effects on growth and tolerance and hypoallergenicity of an amino acid-based formula with synbiotics. *Pediatr Res.* 2014;75:343-51

STUDY 2 Background

Amino acid-based formulas (AAF) have been shown to effectively manage cow milk allergy and resolve symptoms while supporting normal growth. This study was designed to evaluate the hypoallergenicity of an AAF with an added synbiotic blend in a group of subjects with confirmed cow milk allergy (CMA).

Methods

Thirty infants and young children were recruited, all of whom had immunoglobulin E (IgE)-mediated CMA. Hypoallergenicity of an AAF with an added synbiotic blend (Neo-Syn) was determined with double-blind, placebo-controlled food challenges (DBPCFC) as well as a 7-day feeding period. In the DBPCFC, subjects were randomized to either receive Neo-Syn followed by the control hypoallergenic formula, Neocate Infant with DHA and ARA (Neo), or vice versa. Dietary intake and clinical symptoms were monitored.

Results

Thirty infants and children with a confirmed history of IgE-mediated CMA were recruited. A majority of the subjects (23/30) reported other food allergies (see table). All 30 subjects completed the DBPCFC. None of the 30 subjects demonstrated an allergic reaction to either formula in the DBPCFC.

Conclusion

This study shows that an AAF with an added synbiotic blend is hypoallergenic in infants and children with IgE-mediated CMA.

Allergens reported by 23 of 30 subjects in addition to cow milk

Egg	n = 9
Peanut	n = 9
Soy	n = 7
Fish	n = 1
Other food allergies (incl. tree nut, oatmeal, corn, sweet potatoes)	n = 10

Adapted from Harvey et al. 2014.

Neocate with synbiotics was found to be hypoallergenic when compared to a control hypoallergenic formula, Neocate Infant DHA/ARA.*

An amino acid-based formula with prebiotics and probiotics, Neocate Syneo Infant is backed by this clinical trial to be hypoallergenic according to criteria set by the American Academy of Pediatrics.

Translated and adapted from English full text article – publicly available at <http://www.nature.com/pr/journal/v75/n2/full/pr2013211a.html>

* Known in Canada as Neocate DHA & ARA infant formula

Burks AW, Harthoorn LF, van Ampting MTJ, et al. Synbiotics-supplemented amino acid-based formula supports adequate growth in cow's milk allergic infants. *Pediatr Allergy Immunol.* 2015;26:316-22

Background

Cow milk allergy (CMA) places children at risk for insufficient nutrient intake and poor growth. Because of this, the dietary management of CMA in children necessitates a diet that excludes allergens, while also promoting normal growth and development. This study set out to evaluate the growth of infants with CMA consuming a new amino acid-based infant formula (AAF) with an added synbiotic blend (prebiotics and probiotics). Safety was also evaluated.

Methods

This prospective, double-blind controlled study involved full-term infants aged 0-8 months diagnosed with CMA. The infants were randomized to receive either a control AAF (Neocate Infant with DHA and ARA; n = 56) or a test AAF with synbiotics (Neocate + oligosaccharide blend + probiotic *Bifidobacterium breve* M-16V; n = 54). The study duration was 16 weeks and the primary outcome, growth, was assessed using weight, length and head circumference. Secondary outcome measures were parameters that assessed allergic signs and symptoms as well as stool characteristics.

Results

At inclusion, infants were 4.5 ± 2.4 months of age. Results showed that both groups, infants receiving the AAF or the AAF with synbiotics, achieved adequate and similar growth during this study. Based on WHO 2006 growth charts, there were no significant differences (90% CI) between groups in Z-scores (test/control) after 16 weeks: weight ($p = 0.32$), length ($p = 0.21$) and head circumference ($p = 0.40$). There were also no significant differences between the two groups in weight-for-age or length-for-age Z-scores. In addition, both formulas were well tolerated and both reduced symptoms of CMA, with no difference in numbers of adverse events between the two groups.

Conclusions

This study is the first to demonstrate that an AAF with an added synbiotic blend of specific components, suitable for infants with CMA, promotes normal growth, as well as growth in infants with CMA similar to a reference AAF. Neocate with synbiotics and Neocate Infant DHA/ARA were both demonstrated to support normal growth and resolve food allergy symptoms in infants with IgE- and/or non-IgE-mediated CMA.

This large clinical trial studying CMA infants supports that:

- **Both Neocate Syneo Infant and Neocate Infant DHA/ARA* support normal growth and development of CMA infants.**
- **Neocate Syneo Infant is as safe and well tolerated as Neocate Infant DHA/ARA**
- **Neocate Syneo Infant resolves food allergy symptoms as effectively as Neocate Infant DHA/ARA**

Translated and adapted from publicly available abstract - English full text available at <http://onlinelibrary.wiley.com/doi/10.1111/pai.12390/full>
*Known in Canada as Neocate DHA & ARA infant formula

Michaelis LJ, Wopereis H, van Ampting MTJ, et al. An amino acid-based formula with synbiotics affects faecal microbiota in non-IgE mediated cow's milk allergic infants. EAACI Annual Meeting. Jun 11-15; Vienna, Austria. Allergy. 2016;71(S102):58(114)

The ASSIGN Trial Background

Hypoallergenic infant formulas – based on extensively hydrolyzed protein or amino acids - are used in the dietary management of cow milk allergy (CMA) in infants. Research has shown that infants and children with CMA have an imbalanced gut microbiota associated with their allergic condition. This study sought to determine whether an amino acid-based formula (AAF) supplemented with a specific synbiotic blend, designed for CMA patients, will improve the gut microbiota as it develops in CMA subjects.

Methods

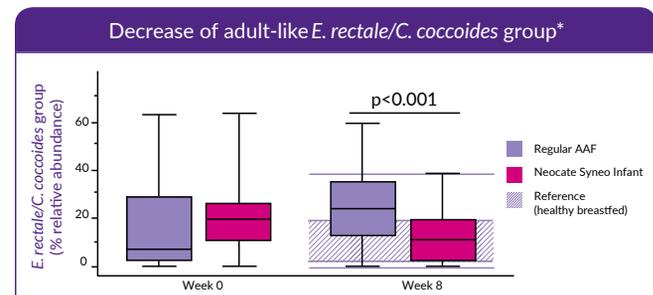
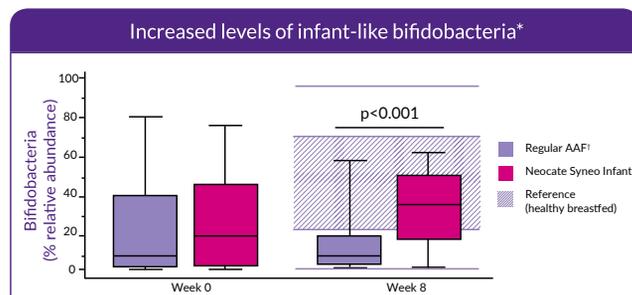
The study was prospective, randomized, double-blind and controlled, lasting 8 weeks (registered as NTR3979). Infants (6.00+/-2.98 months) with non-IgE-mediated CMA were randomized to either a control AAF (n=36) or a test AAF supplemented with a specific synbiotic blend of short-chain fructooligosaccharides (scFOS), long-chain fructooligosaccharides (lcFOS) and *Bifidobacterium breve* M-16V (n=35). As the study was blinded, participants were unaware of the AAF they were assigned. The primary outcome measures were bifidobacteria, as a marker of a gut microbiota of a healthy infant, and the *Eubacterium rectale/Clostridium coccoides* (ER/CC) group, representing an adult-like gut microbial group, as percentages of total fecal bacteria. Secondary outcomes included stool characteristics, fecal short-chain fatty acid (SCFA) levels, fecal secretory IgA levels, and concomitant medication use.

Results

CMA symptoms were primarily gastrointestinal (90% of subjects) as well as dermatological (10% of subjects), and subjects were stratified based on these factors. Sixty subjects completed the 8-week intervention (test n = 28; control n = 32). The study demonstrated that, following an 8-week intervention, test group subjects' fecal microbiota shifted in levels of both *Bifidobacterium* species and the ER/CC group to be closer to levels seen in a reference group of age-matched, healthy breastfed infants vs. control group subjects. Test group subjects demonstrated significantly higher levels of bifidobacteria (35.6%) after 8 weeks compared to control group subjects (26.6%) (p<0.001). The test group also demonstrated significantly lower ER/CC levels (12.1%) compared to the control group (26.6%) (p<0.001). Secondary and clinical outcome measures of the study are pending. Similar numbers of subjects in both groups experienced (serious) adverse events.

Conclusions

This study demonstrated that an AAF with an added specific synbiotic mixture is suitable for CMA infants and will help to rebalance the gut microbiota by significantly increasing fecal bifidobacteria levels and lowering the ER/CC group vs. a standard AAF, bringing the gut microbiota composition closer to that seen in age-matched, healthy breastfed infants*.



Neocate Syneo Infant is an amino acid-based formula with prebiotics and probiotics that has been clinically shown to help address the hidden, underlying gut dysbiosis seen with CMA by bringing the gut microbiota of infants with CMA closer to that of healthy, breastfed infants.

Translated and adapted from publicly available English abstract - <http://onlinelibrary.wiley.com/doi/10.1111/all.12970/epdf> (abstract 114)

Figures adapted from: Candy DCA, van Ampting MTJ, Oude Nijhuis MM, et al. Dietary management of non-IgE mediated cow's milk allergic infants with a synbiotics-supplemented amino acid-based formula: effects on faecal microbiota and clinical symptoms. Poster presented at WCPGHAN Meeting. Oct 5-8; Montréal, Québec. 2016.

* Statistics are based on ANCOVA comparing test vs. control with Week 8 values as outcome, stratification factor (skin or gastrointestinal symptoms) and imputed baseline values as covariate and treatment as fixed effect. The grey shaded area represents the sample 25th to 75th percentile of the reference group (healthy subjects) and the grey horizontal lines represent the minimum and maximum values of this reference group.

AAF = amino acid-based formula; ASSIGN = Amino acid-based formula with Synbiotics – Study in Infants with Gastrointestinal Non-IgE-mediated cow's milk allergy

* Nutricia Advanced Medical Nutrition. Unpublished preliminary report on the primary outcome and safety findings of the ASSIGN trial. Data on file. 2016.

Harvey BM, Eussen SRBM, Harthoorn LF, Burks AW. Mineral intake and status of cow's milk allergic infants consuming an amino acid-based formula. J Pediatr Gastroenterol Nutr. 2017;65:346-9

Purpose

A prospective, randomized, double-blind controlled clinical trial assessed the mineral status of term infants, age 0-8 months at recruitment, diagnosed with CMA consuming an amino acid-based formula (AAF) for 16 weeks.

Methods

Serum levels of minerals routinely assessed in the target population were measured at baseline (n = 82) and following 16 weeks receiving an AAF, Neocate[®], with or without synbiotics (n = 66). Minerals (calcium, phosphorus, chloride, sodium, potassium, magnesium and iron (ferritin)) were analyzed using standard methods, and results were evaluated against reference ranges that were age specific. Individual intakes of estimated energy and minerals were compared to Adequate Intake (AI) levels established by the US Institute of Medicine and European Food Safety Authority.

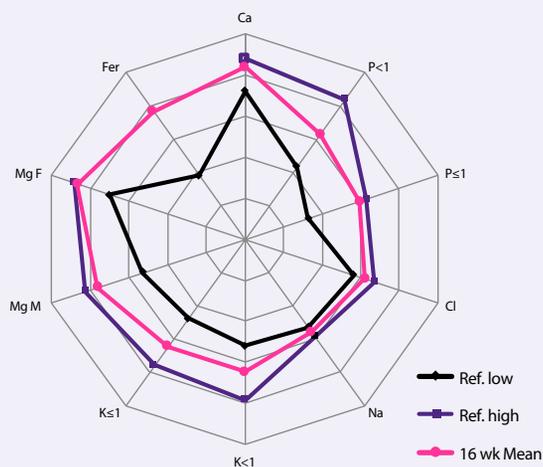
Results

Mean serum mineral levels at baseline and following 16 weeks receiving an AAF were within reference ranges for age. Some individual baseline values were below age-specific reference ranges for calcium, phosphorus, chloride, sodium and ferritin, whereas after 16 weeks only the ferritin level for some individuals remained below the reference range. Mean estimated intakes from formula plus diet for most minerals were above or close to the AIs, suggesting low prevalence of inadequate mineral intakes.

Conclusions

Individual mineral levels at week 16 were all within age-specific ranges, with the exception of ferritin. Previous research in healthy infants also found low levels of serum ferritin of similar prevalence. A vast majority of infants 0-6 months (formula as sole source of nutrition) and aged 6-12 months (formula plus complementary foods) had adequate mineral intakes. This study shows that the AAF Neocate, with or without synbiotics, effectively supported adequate serum status of the selected minerals in cow milk-allergic infants.

Figure 1. Mean blood chemistry parameters after 16 weeks on Neocate (n = 66). Values scaled for visual comparison, with mean 16-week values plotted relative to reference ranges: see open text for actual values and ranges.



Ca = Calcium, P<1 = Phosphorus <1 y, P≥1 = Phosphorus ≥1 y, Cl = Chloride, Na = Sodium, K<1 = Potassium <1 y, K≥1 = Potassium ≥1 y, Mg M = Magnesium Male ≥30 d, Mg F = Magnesium Female ≥30 d, Fer = Ferritin.

This study supports that Neocate Syneo Infant and Neocate Infant* are effective in providing adequate dietary mineral intake and maintaining mineral status in infants with cow milk allergy.

Translated and adapted from publicly available English full text article – http://journals.lww.com/jpgn/Fulltext/2017/09000/Mineral_Intake_and_Status_of_Cow_s_Milk_Allergic.23.aspx

*Known in the US as Neocate Infant DHA/ARA and in Canada as Neocate DHA & ARA infant formula.

de Boissieu D, Matarazzo P, Dupont C. Allergy to extensively hydrolyzed cow milk proteins in infants: identification and treatment with an amino acid-based formula. J Pediatr. 1997;131:744-7

Background

Allergy to extensively hydrolyzed formula (eHF) has been reported in infants with immediate hypersensitivity reactions such as anaphylactic shock or bloody diarrhea. The hypothesis of this study was that allergy to eHFs might not be uncommon in association with cow milk allergy (CMA), even in absence of severe immediate reactions or multiple food allergies.

Methods

Sixteen infants (1 to 16 months) who had adverse reactions to cow milk were referred because of persistent gastrointestinal symptoms in spite of cow milk elimination with an eHF. To identify eHF allergy, a nutritionally complete amino acid-based infant formula (AAF), Neocate, was initiated. An oral challenge was performed with an eHF after this exclusion period. Weight was monitored and parents recorded symptoms.

Results

In 13 infants, feeding with an AAF decreased gastrointestinal symptoms within 3 days and improved atopic dermatitis score ($p < 0.05$). All 13 infants experienced significant weight gain and in all of these infants the challenge with an eHF yielded positive reactions. The three infants whose symptoms did not respond to an AAF had negative reactions to the eHF challenge.

Conclusion

Allergy to eHF must be considered in those infants allergic to cow milk whose symptoms do not fully improve on an eHF, for example persistent gastrointestinal symptoms and/or failure to thrive. The use of an AAF provides a safe alternative.

Feeding an AAF (Neocate) resolved non-cutaneous food allergy symptoms within 3 days, significantly improved atopic dermatitis score ($p < 0.05$) and significantly improved weight gain for infants allergic to an eHF

Vanderhoof JA, Murray ND, Kaufman SS, et al. Intolerance to protein hydrolysate infant formulas: an underrecognized cause of gastrointestinal symptoms in infants. J Pediatr. 1997;131:741-4

Background

Cow milk protein is the first protein fed to many infants and cow milk allergy (CMA) is the most common food allergy in infants. For CMA infants a soy or casein hydrolysate formula (CHF) is trialed, but 30-50% of infants with CMA also being allergic to soy protein and a sub-group of infants trialed on CHF do not have complete symptom improvement or resolution. The purpose of this study was to evaluate the clinical response of CMA infants symptomatic on CHF to an amino acid-based formula (AAF).

Methods

Twenty eight infants were enrolled from 22 to 173 days of age; all were unresponsive to CHF after an average of 40 days (10 to 173 days), defined as persistence of one or more of the following symptoms: bloody stools, vomiting, diarrhea, irritability and poor weight gain, or a combination of these symptoms (see table). Sigmoidoscopy with rectal biopsy was performed in all infants to include those with inflammatory changes. Infants then received an AAF (Neocate) for 14 days.

Results

Following 2 weeks of management with an AAF, 25 infants showed symptom resolution. These infants underwent an oral challenge with a CHF: 8/25 tolerated the CHF, but the remaining 17/25 infants demonstrated symptom recurrence. The features seen on histologic examination ranged from normal to eosinophilic infiltration.

Conclusion

In conclusion, some infants who appear to exhibit formula protein-induced colitis do not respond to CHF. These infants may demonstrate symptom resolution when managed with an amino acid-based infant formula.

Persisting symptoms in 28 infants on CHF (mean CHF duration 40 days: range 10-173)

Persistent symptoms	n
Blood in stools	15
Diarrhea	12
Vomiting	10
Poor weight gain	4
Irritability/crying	18

Adapted from Vanderhoof et al. 1997

Feeding an AAF (Neocate) resolved CMA-related gastrointestinal symptoms within 14 days in infants with unresolved symptoms on a CHF

Translated and adapted from English full text article - abstract publicly available at <http://www.ncbi.nlm.nih.gov/pubmed/9403656>

Berni Canani R, Nocerino R, Frediani T, et al. Amino acid-based formula in cow's milk allergy: long-term effects on body growth and protein metabolism. J Pediatr Gastroenterol Nutr. 2017;64:632-8

Background:

There is limited research into the long-term effects of the use of amino acid-based formulas (AAF) in the dietary management of infants and children with cow milk allergy (CMA). This research aims to study the effects on growth and protein metabolism in CMA children managed using an AAF or using an extensively hydrolyzed whey formula (eHFW), with a reference group of healthy controls.

Methods:

A multicenter, randomized controlled trial with 12-month duration was conducted in outpatient subjects with CMA (5-12 months of age). Subjects were randomized to receive either an AAF (group A) or eHFW (group B), and compared to healthy controls (group C). Groups A and C switched to an equivalent pediatric formula at age >12 months. Subjects were evaluated clinically at baseline (enrolment, T0), and after 3, 6, and 12 months (T3, T6, T12). For subjects with CMA at T0 and T3, serum lab values were measured (albumin, urea, total protein, retinol-binding protein, and insulin-like growth factor 1).

Results:

The study was completed by 21 subjects in group A (38.1% female, 6.5 ± 1.5 months of age), 19 in group B (42.1% female, 7 ± 1.7 months of age) and 25 subjects in group C (52% female, 5.5 ± 0.5 months of age). Baseline (T0) weight z scores for groups A and B were comparable (-0.74 and -0.76), but different as compared to group C (-0.17, $P < 0.05$). By T12, weight z scores were similar between all three groups (NS). No significant changes in protein metabolism were detected in subjects of groups A and B.

Conclusion:

Management of children with CMA using an AAF long-term is safe and supports adequate growth.

Using age-appropriate AAFs (Neocate formulas) to manage CMA for 12 months, from infancy through early childhood, has been shown to support adequate protein status and promote normal growth comparable to healthy children

Translated and adapted from publicly available English abstract - <http://www.ncbi.nlm.nih.gov/pubmed/27437928>

Sampson HA, James JM, Bernhisel-Broadbent, J. Safety of an amino acid-derived infant formula in children allergic to cow milk. Pediatrics. 1992;90:463-5

Background

Patients with IgE-mediated allergy to cow milk and cow milk-induced enterocolitis syndrome may react to extensively hydrolyzed formula (eHF). The availability of an amino acid-based infant formula for such cases would be beneficial. The aim of this study was to assess whether Neocate is safe for children with cow milk allergy.

Methods

Children aged between 11 months to 12 years (n=28) with documented intolerance to cow milk were enrolled. Twenty seven had previously undergone a double-blind, placebo-controlled food challenge (DBPCFC) to confirm allergy to cow milk. The remaining subject had experienced anaphylaxis and was not challenged. Skin-prick tests were carried out for cow milk, Neocate, three hydrolyzed formulas and histamine/saline (as a control). All patients underwent DBPCFC to cow milk, AAF (Neocate), and eHF (placebo), in random order. Patients tolerating AAF were offered 6 months of open feeding.

Results

All patients positively reacted to cow milk on skin-prick test. Positive skin-prick test reactions were seen to all formulas, with the fewest to Neocate (see table). All children tolerated Neocate in both the DBPCFC and the subsequent open feeding challenge.

Conclusion

Neocate is "hypoallergenic" according to recommendations made in 1990 by the American Academy of Pediatrics' Subcommittee on Nutrition and Allergic Disease. Neocate is well tolerated by children with an allergy to cow milk and may be the safest choice for children with more severe milk allergy.

Skin prick test results to different formula carried out in 16 children

Formula	Reactions (n=16)
Neocate	3/16
eHF 1	5/16
eHF 2	8/16 (50%)
Partial hydrolysate	16/16 (100%)

Adapted from Sampson et al 1992

Neocate is hypoallergenic, well tolerated by children who are allergic to cow milk, and may be safer than eHF in those with more severe allergy to milk

Translated and adapted from English full text article - abstract publicly available at <http://pediatrics.aappublications.org/content/90/3/463>

Multiple Food Allergies (MFA) in Infants and Children

Publication	Title	Study Purpose	Methodology	Result/Conclusion	Page number
Infants					
Hill DJ et al. J Allergy Clin Immunol. 1995;96:386-94.	Challenge confirmation of late-onset reactions to extensively hydrolyzed formulas in infants with multiple food protein intolerance	To observe the effect of food challenges in infants with reported hypersensitivity to hypoallergenic formulas	Infants were given Neocate for 2 months and then underwent a 7-day, double blind, placebo-controlled challenge with the eHF previously best tolerated	AAF (Neocate) was an effective substitute formula for infants with late-onset adverse reactions to eHF, soy and other foods, with remission of symptoms within 14 days	Abstract Page 15
de Boissieu D et al. J Pediatr. 2002;141:271-3.	Allergy to extensively hydrolyzed cow's milk proteins in infants: safety and duration of amino acid-based formula	A study to assess the safety of using AAF long-term and analyze the potential duration of its use according to the clinical presentation	Infants with CMA who were intolerant to eHF and soy were switched to an AAF and challenged after 1 month	AAF (Neocate) proved to be safe, with infants gaining weight and length. Restricted diets with AAF may be required for longer durations when multiple food allergies exist	Abstract Page 16
Children					
Hill DJ et al. J Pediatr. 1999;135:118-21.	The natural history of intolerance to soy and extensively hydrolyzed formula in infants with multiple food protein intolerance	To observe the long-term effect of using an AAF in children with MFA	Children were followed for up to three years following commencement to AAF, and growth was monitored	AAF is tolerated by infants with MFA who are intolerant to soy and eHF, and improves growth for those infants who experience failure to thrive due to MFA	Abstract Page 17

AAF = amino acid-based formula; eHF = extensively hydrolyzed formula; MFA = multiple food allergies



Hill DJ, Cameron DJ, Francis DE, et al. Challenge confirmation of late-onset reactions to extensively hydrolyzed formulas in infants with multiple food protein intolerance. J Allergy Clin Immunol. 1995;96:386-94

Background

Many infants with cow's milk protein intolerance have adverse reactions to soy, casein and whey hydrolysate formula and to other foods. The recent development of Neocate, a hypoallergenic, nutritionally complete infant formula composed of individual amino acids and other nutrients, has enabled these infants to be stabilized.

Objective

We observed the effect of food challenges in infants with reported hypersensitivity to hypoallergenic formulas.

Methods

Eighteen infants (median age, 7 1/2 months) were given Neocate formula for 2 months and then underwent a 7-day double-blind placebo-controlled challenge with the formula previously best tolerated.

Results

In 12 of the 18 infants, irritability, vomiting, diarrhea, and/or eczema flares developed during the formula challenge. In two patients symptoms developed immediately, but in the remainder adverse reactions evolved within 7 days (range, 4 to 7 days). Adverse reactions were to soy formula (six patients), whey hydrolysate (two), and casein hydrolysate (four). When infants were 12 months of age, parents reported adverse reactions after the ingestion of other low allergen foods (median, six; from a panel of 10 such foods).

Conclusion

A group of infants with late-onset adverse reactions to soy, extensively hydrolyzed casein, and whey formulas and to other foods has been identified. Neocate formula proved to be an effective substitute formula for these patients.

An AAF (Neocate) was effective for the dietary management of infants with multiple food allergies, with remission of symptoms within 14 days

Translated from publicly available English abstract - full text article publicly available at [http://www.jacionline.org/article/S0091-6749\(95\)70058-7/pdf](http://www.jacionline.org/article/S0091-6749(95)70058-7/pdf)

de Boissieu D, Dupont C. Allergy to extensively hydrolyzed cow's milk proteins in infants: safety and duration of amino acid-based formula. J Pediatr. 2002;141:271-3

Background:

Approximately 10% of children with cow milk allergy do not respond to an extensively hydrolyzed formula (eHF). Amino acid-based formulas (AAF) are needed by those patients who don't respond to eHFs. The purpose of this survey was to assess the safety of long-term feeding with an AAF in infants and to analyze the potential duration of its use according to the clinical presentation.

Methods:

Fifty two infants with allergies to cow milk and extensively hydrolyzed formula (eHF) (including the cohort of de Boissieu, et al. 1997) were followed up for as long as 69 months. Eighteen patients were solely allergic to eHF, and the remaining to eHF plus additional foods. Infants received an AAF for 1 month followed by an oral challenge with the eHF previously used. Height and weight were assessed on all subjects at the beginning and end of study period.

Results:

The AAF was used for 11.4±7.9 months and proved to be safe for all subjects. Infants demonstrated an overall increase in both length and weight, as assessed by Z scores. Eleven children did not tolerate cow milk by the end of the survey period. The median age of cow milk tolerance was 20.5 months (see table for further tolerance data). Children with isolated eHF intolerance were diagnosed earlier and tolerated cow milk earlier than those with multiple food allergies.

Conclusion:

Long-term use of AAF was safe for patients allergic to both cow milk and eHF. In patients allergic to eHF plus additional foods, tolerance of cow milk may occur later, indicating that an AAF may be required for longer duration for these patients.

Age at which cow milk protein tolerance was achieved

Age	n
1 year of age	8
1 to 2 years of age	22
2 to 3 years of age	8
After 3 years of age	3
Not tolerated by end of study	11

Median age of tolerance was 20.5 months

Adapted from de Boissieu et al 2002

Long-term use of an amino acid-based formula (Neocate) supports growth and is safe for infants with allergies to eHF and with multiple food allergies. In multiple food allergies (including eHF), an AAF may be needed for a longer duration

Translated and adapted from English full text article - abstract publicly available at <http://www.ncbi.nlm.nih.gov/pubmed/12183726>

Hill DJ, Heine RG, Cameron DJ, et al. The natural history of intolerance to soy and extensively hydrolyzed formula in infants with multiple food protein intolerance. J Pediatr. 1999;135:118-21

Background

This report summarizes the outcome from an initial cohort of 18 infants with multiple food allergies (MFA) - intolerant to soy and eHF - who were followed up to 3 years of age.

Methods

All 18 infants were started on an amino acid-based formula (AAF - Neocate). Participants were followed regularly until 3 years of age. Growth was monitored, and most participants were re-challenged with formulas they had previously not tolerated.

Results

By 24 months of age most patients tolerated non-formula foods. By 36 months of age only 3 patients still required AAF for ongoing nutritional support. The patients with failure to thrive had achieved catch-up growth within 6 to 12 weeks of beginning AAF feeding.

Conclusion

All infants in this research with MFA responded to dietary management with an AAF. Some patients required long-term nutritional support with an AAF. Infants presenting with failure to thrive caused by MFA were able to achieve normal growth following initiation of an AAF.

Infants presenting with multiple food allergy (including eHF & soy) achieved normal growth into early childhood with an AAF (Neocate). The authors attributed the improved growth to "improved delivery of protein and energy and control of nutrient loss from vomiting and diarrhea."

Translated and adapted from English full text article - abstract publicly available at <http://www.ncbi.nlm.nih.gov/pubmed/10393618>

Atopic Dermatitis (AD) related to food allergies

Publication	Title	Study Purpose	Methodology	Result/Conclusion	Page number
Infants					
Isolauro E et al. J Pediatr. 1995; 127:550-7.	Efficacy and safety of hydrolyzed cow milk and amino acid-derived formulas in infants with cow milk allergy	To determine the antigenicity, nutritional adequacy and growth-promoting efficacy of eHF or AAF formulas in infants with CMA [a two part study]	Part I looked at the antigenicity of different formulas. In part II 74 infants with atopic dermatitis and CMA were randomized to either whey extensive hydrolysate (We) (n=22) or AAF (Neocate) (n=23) and followed-up for 9 months	The antigenicity was highest in the partial hydrolysate formula and lowest in Neocate. Both formulas (eHF; Neocate) were clinically and biochemically tolerated. AAF (Neocate) may be preferable for infants with multiple food allergies, especially to maintain normal growth	Abstract Page 19
Niggemann B et al. Pediatr Allergy Immunol. 2001;12:78-82.	Prospective, controlled, multi-center study on the effect of an AAF in infants with cow's milk allergy and atopic dermatitis	To study the efficacy of AAF compared to eHF on the growth and clinical symptoms of infants with CMA and AD	73 infants with AD and CMA were randomly assigned to receive an AAF (Neocate, n=31) or eHF (n=42) and followed up for 6 months	Both formulas showed significant improvement of atopic dermatitis (p<0.0001). Increase in length SD was only apparent in the AAF-fed group (p<0.0004)	Abstract Page 20

AAF = amino acid-based formula; AD = atopic dermatitis; CMA = cow milk allergy; eHF = extensively hydrolyzed formula



Isolauri E, Sütas Y, Mäkinen-Kiljunen S, et al. Efficacy and safety of hydrolyzed cow milk and amino acid-derived formulas in infants with cow milk allergy. *J Pediatr.* 1995;127:550-7

Objective

To determine the antigenicity, nutritional adequacy, and growth-promoting efficacy of protein hydrolysate or amino acid-derived formulas in infants with cow milk allergy.

Study Design

Several protein hydrolysate or amino acid-derived formulas were graded for beta-lactoglobulin content and skin reactivity in 74 atopic children with cow milk allergy proved by a double-blind, placebo-controlled challenge. A randomized, prospective follow-up study of 9 months included 22 infants with a mean age of 6 months (95% confidence interval, 4 to 7), who were fed an extensively hydrolyzed whey formula (group We), and 23 infants with a mean age of 17 (95% confidence interval, 4 to 7) months, who were given an amino acid-derived formula (group AA).

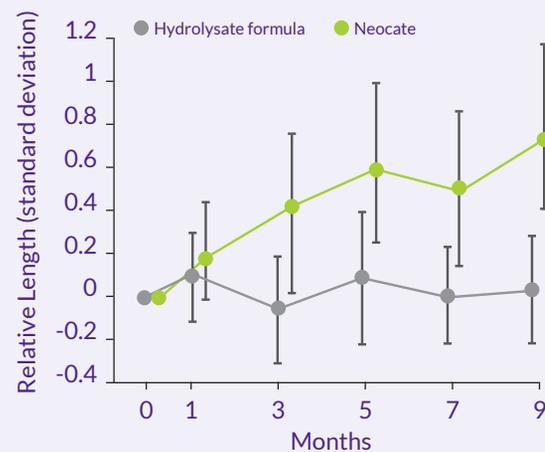
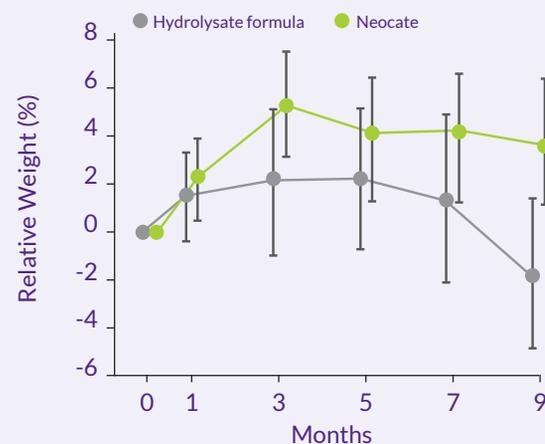
Results

Both formulas were clinically and biochemically tolerated. The mean concentration of essential amino acids in plasma was lower in group We but higher in group AA compared with values for breast-fed control infants ($p = 0.001$). There was a different trend between the groups in weight ($p = 0.09$) and length ($p = 0.006$). Growth was promoted in group AA during the follow-up; it was constant during the first months, followed by a gradual decline in rate in group We. In both groups, atopic eczema improved significantly and progressively, and a downward trend was found in serum total and milk-specific IgE concentrations, proving the efficacy of both formulas.

Conclusions:

Extensively hydrolyzed formulas are safe and effective for most infants; an amino acid-derived formula may be preferable for infants with multiple food allergies, especially for the maintenance of normal growth.

Growth of infants (weight and length) with AD and CMA in those fed eHF versus AAF



Adapted from Isolauri et al 1995

Adapted from Isolauri et al 1995

Neocate helps resolve atopic dermatitis related to food allergies and may be the preferred hypoallergenic formula for infants with multiple food allergies, especially to maintain normal growth

Translated from English abstract - available at [https://www.jpeds.com/article/S0022-3476\(95\)70111-7/fulltext](https://www.jpeds.com/article/S0022-3476(95)70111-7/fulltext)
AD = atopic dermatitis; CMA = cow milk allergy; AAF = amino acid-based formula

Niggemann B, Binder C, Dupont C, et al. Prospective, controlled, multi-center study on the effect of an amino-acid-based formula in infants with cow's milk allergy/intolerance and atopic dermatitis. *Pediatr Allergy Immunol.* 2001;12:78-82

Background

Food allergy and atopic dermatitis (AD) are often associated with each other. An allergy to cow milk - a key source of multiple nutrients in early childhood - is managed through complete dietary avoidance of cow milk protein, which may cause nutrient deficiencies and inhibit growth. There has been little research comparing the use of amino-acid-based formula (AAF) in infants who have cow milk allergy to extensively hydrolyzed cow milk formula (eHF).

Methods:

Seventy-three infants, aged 1-10 months, with proven cow milk allergy and AD were enrolled in a prospective, controlled, multi-center trial to study the effect of AAF compared to eHF on clinical symptoms and growth. Children were randomized to receive an AAF (Neocate) or an eHF. Over a 6-month time period, participants were monitored for clinical symptoms of AD (using the SCORAD index), dietary intake, length, and weight. Between groups there were no statistically significant differences at entry in gender, age, total immunoglobulin E (IgE), specific IgE, SCORAD or family history for atopy.

Results:

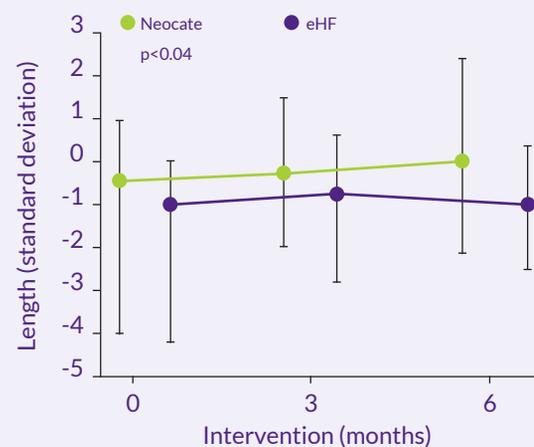
Both the AAF and eHF groups demonstrated a significant improvement in the SCORAD index ($p < 0.0001$). There was a statistically significant ($p < 0.04$) increase in the standard deviation score for length for the AAF group, but no such difference was seen for the eHF group, despite similar energy intakes. Weight-for-length values in both groups were stable.

Feeding an AAF (Neocate) to infants with CMA and AD significantly increased length ($p < 0.04$) compared to feeding an eHF, despite similar energy intakes

Conclusions:

Both eHF and AAF lead to significant clinical improvement for infants with cow milk allergy. Only an AAF supported improved length, so can be seen as a beneficial alternative for infants who have severe cow milk allergy.

Length data during management with eHF versus AAF (median and standard deviation range)



Adapted from Niggemann et al 2001.

Gastroesophageal Reflux (GER)* related to food allergies

*Also referred to as Gastro-Oesophageal Reflux/Disease (GOR/D)

Publication	Title	Study Purpose	Methodology	Result/Conclusion	Page number
Infants					
Hill DJ et al. J Pediatr. 2000;136:641-7.	Role of food protein intolerance in infants with persistent distress attributed to reflux esophagitis	This study examines the effect of AAF on infant distress and symptoms of GER in infants who fail to respond to eHF and anti-reflux medications	Infants with persistent distress and vomiting failing anti-reflux medication and eHF received 3 months of AAF. DBPC formula challenge of AAF versus previously best-tolerated formula	A marked reduction of distressed behavior was shown in all infants within two weeks of using an AAF. Use of an AAF may reduce distressed behavior and symptoms of GER in infants with food allergies	Abstract Page 22
Thomson M et al. Pediatr Asthma Allergy Immunol. 2006;19:205-13.	Effect of an amino acid-based milk - Neocate® - on gastro-oesophageal reflux in infants assessed by combined intraluminal impedance/pH	To investigate the influence of an AAF on GER in infants by using a combined pH and intraluminal esophageal impedance measurement	Infants with symptoms of GER underwent two 24-hour studies of intra-esophageal 6 channel impedance and dual-channel pH monitoring before and after 14 days of an AAF (Neocate)	10/11 parents reported a significant reduced reflux score when AAF was used (p=0.001). Other markers of reflux were not significantly different	Abstract Page 23
Borrelli O et al. J Pediatr. 2012;161:476-81.	Cow's milk challenge increases weakly acidic reflux in children with cow's milk allergy and gastroesophageal reflux disease	To assess the effect of dietary exclusion and a cow milk challenge on reflux in infants diagnosed with both CMA and suspected GERD	Infants with CMA and GERD were monitored for 96 hours total using a multichannel esophageal impedance-pH device while on an amino acid-based formula and while on a cow milk-based formula	Consumption of cow milk-based formula by infants diagnosed with CMA and suspected GERD resulted in an increase of weakly acidic reflux events	Abstract Page 25
Children					
Miele E et al. J Pediatr Gastroenterol Nutr. 2002;35:314-9.	Clinical response to amino acid-based formula in neurologically impaired children with refractory esophagitis	To evaluate the efficacy of a dietary trial of Neocate in neurologically impaired children unresponsive to medical and surgical treatment for GERD	Children with CP and long-standing GERD were fed an AAF (Neocate) for 4 weeks. Endoscopic biopsy and sugar permeability tests were performed before and after the formula trial	AAF (Neocate) significantly improved endoscopic (p<0.01) and histologic (p<0.05) findings in neurologically impaired (CP) children with non-responsive GERD	Abstract Page 26

AAF = amino acid-based formula; CP = cerebral palsy; DBPC = double blind placebo controlled; eHF = extensively hydrolyzed formula; GER = gastroesophageal reflux; GERD = gastroesophageal reflux disease



Hill DJ, Heine RG, Cameron DJ, et al. Role of food protein intolerance in infants with persistent distress attributed to reflux esophagitis. J Pediatr. 2000;136:641-7

Background

Distressed behavior is common in infants and is often attributed to gastroesophageal reflux (GER) or food protein intolerance.

Objective

To examine the effect of a hypoallergenic amino acid-based infant formula (AAF) on distressed behavior and GER symptoms in infants who failed to respond to extensively hydrolyzed formula and anti-reflux medications.

Study Design

Nineteen distressed infants (9 boys and 10 girls; median age, 5.0 months) with presumed GER underwent gastroscopy (n = 17) and esophageal 24-hour pH monitoring (n = 14). Double-blind placebo-controlled (DBPC) formula challenges of AAF versus previously best tolerated formula were conducted.

Results

Nine infants had histologic evidence of esophagitis, and 9 had inflammatory changes in the stomach and/or duodenum. Symptoms remitted in all infants within 2 weeks of the start of feeding with AAF. On DBPC challenge after a median period of 3 months of receiving AAF, 12 infants were intolerant to active formula (distress score, 287 vs 580 min/wk, P = .01; symptom score, 23.1 vs 36.1, P = .03). Seven infants did not relapse and were considered tolerant (distress score, 470 vs 581, P = .77; symptom score, 29.5 vs 20.2; P = .89).

Conclusion

Treatment with AAF may reduce distressed behavior and symptoms of GER in infants with food protein intolerance.

Feeding an AAF (Neocate) for 2 weeks achieved remission of GER symptoms non-responsive to management, with a marked reduction in infant distress and vomiting

Translated from English abstract - publicly available at [https://www.jpeds.com/article/S0022-3476\(00\)86337-4/pdf](https://www.jpeds.com/article/S0022-3476(00)86337-4/pdf)

Thomson M, Wenzl TG, Fox AT, et al. Effect of an amino acid-based milk - Neocate® - on gastro-oesophageal reflux in infants assessed by combined intraluminal impedance/pH. *Pediatr Asthma Allergy Immunol.* 2006;19(4):205-13

Background

Gastro-esophageal reflux (GER) is common in infants, with possible symptoms including irritability, failure to thrive, anemia, and aspiration pneumonia. Multiple food antigens are known to cause GER, with cow milk among the most common. For infants, symptoms of primary GER can mimic those of GER precipitated by cow milk allergy (CMA), which resolves with dietary exclusion of cow milk. Mechanisms proposed to explain the role of cow milk protein in eliciting GER in infancy remain hypothetical. This research used a new monitoring technique - combined intraluminal impedance/pH - and a parental questionnaire to explore the impact of amino acid-based formula (Neocate) on GER in infants.

Methods

Eleven exclusively bottle-fed infants (median 5 months) with symptoms suggestive of GER were recruited. Most participants (8/11) were suspected to be at high risk for CMA based on family and personal history. Analysis of intraluminal impedance/pH testing was completed at enrolment (on standard diet) and following a 14-day period of diet limited to Neocate formula. Reflux parameters measured included number of reflux events, pH, reflux events following feeds, and reflux duration.

Results

Parent reports of reflux revealed a significant decrease in reflux symptom score for 10/11 infants after 14 days of Neocate ($p = 0.001$). Improvement was more significant ($p = 0.0019$) among the 8 infants viewed at high risk of allergic disease. No significant differences were found among the impedance/pH results.

Conclusions

Despite a lack of evidence of decreased GER episodes for infants with symptoms suggesting GER following 14 days on Neocate, parents perceived an improvement in GER symptoms. This was more prominent in the infants judged at high risk of allergic disease.

Parent reports revealed a significant improvement in reflux score when on Neocate ($p=0.001$). Other markers of reflux were not significantly different

Translated and adapted from English full text article – abstract publicly available at <http://online.liebertpub.com/doi/10.1089/pai.2006.19.205>



Borrelli O, Mancini V, Thapar N, et al. Cow's milk challenge increases weakly acidic reflux in children with cow's milk allergy and gastroesophageal reflux disease. J Pediatr. 2012;161:476-81

Objective

To assess and compare the pattern of reflux in a selected population of infants with cow's milk (CM) allergy (CMA) and suspected gastroesophageal reflux disease (GERD) while on dietary exclusion and following challenge with CM.

Study Design

Seventeen children (median age: 14 months) with a proven diagnosis of CMA and suspected GERD underwent 48-hour multichannel intraluminal impedance-pH monitoring. For the first 24 hours, the infants were kept on amino acid-based formula, and for the subsequent 24 hours, they were challenged with CM.

Results

The total reflux episodes and the number of weakly acidic episodes were higher during CM challenge compared with the amino acid-based formula period [total reflux episodes: 105 (58-127.5) vs 65 (39-87.5), $P < .001$; weakly acidic episodes: 53 (38.5-60.5) vs 19 (13-26.5), $P < .001$; median (25th-75th)]. No differences were found for either acid or weakly alkaline episodes (not significant). The number of weakly acidic episodes reaching the proximal, mid, and distal esophagus was higher during CM challenge ($P < .001$). No differences were found in either acid exposure time or number of long-lasting episodes (not significant).

Conclusion

In children with CMA and suspected GERD, CM exposure increases the number of weakly acidic reflux episodes. CM challenge during 48-hour multichannel intraluminal impedance-pH monitoring identifies a subgroup of patients with allergen-induced reflux, and in selected cases of children with CMA in whom GERD is suspected, its use could be considered as part of diagnostic work-up.

Use of an AAF for patients with CMA-induced gastroesophageal reflux may reduce reflux episodes

Translated from English abstract. Article publicly available at [http://www.jpeds.com/article/S0022-3476\(12\)00258-2/pdf](http://www.jpeds.com/article/S0022-3476(12)00258-2/pdf)

Miele E, Staiano A, Tozzi A, et al. Clinical response to amino acid-based formula in neurologically impaired children with refractory esophagitis. J Pediatr Gastroenterol Nutr. 2002;35:314-9

Background

Conventional management of gastroesophageal reflux disease (GERD) is less effective in infants and children with neurological impairment. In other populations, the use of amino acid-based formulas (AAF) has been shown to improve chronic digestive symptoms and esophageal histology that doesn't respond to conventional management. This study aimed to assess the effectiveness of a trial of AAF in neurologically impaired children who had not responded to conventional therapy for GERD.

Methods

Children (n = 9; median age 44 months) affected by cerebral palsy associated with severe brain damage were recruited. All had long-standing history of GERD non-responsive to standard anti-reflux therapies. Subjects were feed an AAF (Neocate) for at least 4 weeks. All subjects underwent endoscopy prior to and following the dietary intervention, including biopsy of the esophagus, and an intestinal permeability test with mannitol and cellobiose. GERD was diagnosed based on microscopic esophageal changes.

Results

Prior to dietary intervention, 7 subjects had moderate esophagitis and 2 subjects mild esophagitis, based on conventional histologic criteria. Results of the intestinal permeability test were abnormal for 5/9 subjects. The dietary intervention with an AAF resulted in resolution of long-term symptoms for 7/9 subjects. Additionally, following trialing an AAF, there were findings of significant improvement in endoscopy (p <0.01) and histology (p<0.005). Symptoms remained under control at 6-month follow up, following gradual reintroduction of other foods, with the exception of cow milk proteins.

Conclusion

A trial of an elimination diet with an AAF in children with neurological impairment who have not responded to standard anti-reflux therapies may immediately and sustainably improve chronic digestive symptoms and esophagitis, proven both on endoscopy and histology.

Feeding an AAF (Neocate) significantly improved endoscopic (p<0.01) and histologic (p<0.05) findings in neurologically impaired children with refractory esophagitis

Translated and adapted from English full text article - abstract publicly available at <http://www.ncbi.nlm.nih.gov/pubmed/12352519>

Eosinophilic Esophagitis (EoE) in Infants, Children and Adults

Publication	Title	Study Purpose	Methodology	Result/Conclusion	Page number
Infants and Children					
Kelly KJ et al. Gastroenterology. 1995;109:1503-12.	Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula	To investigate whether unremitting symptoms of GER and biopsy abnormalities may be associated with the ingestion of certain foods	Children with a long history of GER unsuccessfully treated using the normal anti-reflux agents and confirmed by endoscopic biopsy were fed an AAF for a minimum of 6 weeks	An AAF (Neocate infant and pediatric formulas) showed statistically significant reduction in the average number of intraepithelial eosinophils (p=0.005) after 6 weeks	Abstract Page 28
Markowitz JE et al. Am J Gastroenterol. 2003;98:777-82.	Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents	To define a population of EoE patients and assess their response to an amino acid-based diet	Children with GER and esophageal eosinophilia resistant to proton pump after 3 months were placed on an AAF for 1 month, followed by repeat EGD	On average 8.5 days of dietary management with an AAF (Neocate) significantly reduced symptoms in EoE patients (p<0.01). Median esophageal eosinophils decreased from 33.7 to 1.0 (p<0.01)	Abstract Page 29
Liacouras CA et al. Clin Gastroenterol Hepatol. 2005;3:1198-206.	Eosinophilic esophagitis: a ten year experience in 381 children	To evaluate all patients with EoE over a 10-year period	A retrospective review evaluated children with EoE over a 10 year period to explore results of various treatments	Removal of dietary antigens significantly improved clinical symptoms and esophageal histology in 98% of children with EoE - an AAF more significantly reduced eosinophils vs. selective food elimination (p < 0.05)	Abstract Page 30
Rubinstein E et al. J Pediatr Gastroenterol Nutr. 2014;59:317-20.	Comparison of 2 delivery vehicles for viscous budesonide to treat eosinophilic esophagitis in children	To examine if Neocate Nutra as a delivery agent for OVB for children is at least as effective in managing EoE as Splenda®	A retrospective study - children who chose to prepare OVB with Splenda (N=46) or with Neocate® Nutra (N=14) were monitored for histologic response	Neocate Nutra represents an alternative OVB mixing agent that is palatable, innovative and effective for families who prefer not to use the amounts of Splenda called for in the standard recipe	Abstract Page 31
Adults					
Warners MJ et al. Aliment Pharmacol Ther. 2017;45:777-87.	Elemental diet decreases inflammation and improves symptoms in adult eosinophilic esophagitis patients	To assess the effectiveness of an elemental diet using a flavored liquid AAF (Neocate® Splash) in the management of adult patients with EoE	21 adult patients with active EoE and dysphagia were managed with an AAF in a 4-week, prospective study	17/21 (81%) successfully completed the study. Complete histologic remission was achieved in 12/17 (81%) and 15/17 (88%) became completely asymptomatic	Abstract Page 32
Warners MJ et al. Am J Gastroenterol. 2017;1-11.	Esophageal and small intestinal mucosal integrity in eosinophilic esophagitis and response to an elemental diet	To evaluate the effect of an AAF (Neocate Splash) on eosinophilic inflammation and esophageal and duodenal mucosal integrity	17 adults with EoE were managed with an AAF for 4 weeks. Pre- and post-endoscopy results were compared. Endoscopic results in 8 healthy controls were compared to patients with EoE to evaluate esophageal and small bowel integrity	An AAF restored mucosal integrity in the absence of food allergen exposure. Small intestinal integrity was not impaired in adult EoE patients	Abstract Page 33

AAF = amino acid-based formula; EGD = esophagogastroduodenoscopy; EoE = eosinophilic esophagitis; GER = gastroesophageal reflux; OVB = oral viscous budesonide

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Kelly KJ, Lazenby A, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology*. 1995;109:1503-12

Background & Aims

Treatment for gastroesophageal reflux may be ineffective in patients with an eosinophilic infiltration of the esophagus. The aim of this study was to investigate whether unremitting symptoms of gastroesophageal reflux and biopsy abnormalities of the esophagus may be associated with the ingestion of certain foods.

Methods

Ten children previously diagnosed with gastroesophageal reflux by standard testing with long-standing symptoms (median, 34.3 months; range, 6-78 months) despite standard anti-reflux therapies, including Nissen fundoplication in 6 patients, were fed the elemental formulas Neocate or Neocate-1-Plus (Scientific Hospital Supplies Inc., Gaithersburg, MD) for a minimum of 6 weeks. Each child had repeat endoscopy followed by open food challenges.

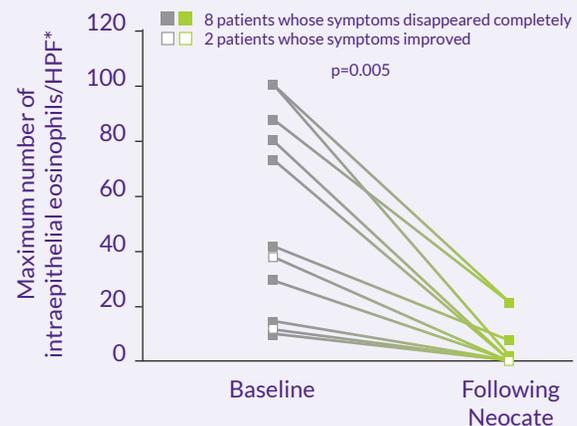
Results

While receiving the formulas, patients had either resolution ($n = 8$) or improvement ($n = 2$) of symptoms. On follow-up esophageal biopsy, the maximal intraepithelial eosinophil counts decreased significantly before (median, 41; range, 15-100) to after (median, 0.5; range, 0-22) the formula trial ($P = 0.005$). Other reactive epithelial changes of the esophageal mucosa also improved significantly. All patients redeveloped their previous symptoms on open food challenges.

Conclusion

Chronic gastrointestinal symptoms and histological changes of the esophagus unresponsive to standard treatments for gastroesophageal reflux were improved by the use of elemental formulas. Symptoms recurred when specific dietary proteins were reintroduced during open food challenges. The mechanism of these observations is unknown.

Maximum intraepithelial esophageal eosinophil levels in children pre- and post-dietary intervention



Adapted from Kelly et al 1995

10 patients (aged 8 months to 12.5 years) with persistent eosinophilic esophagitis. After transitioning to Neocate for at least 6 weeks.

Feeding an AAF (Neocate) for at least 6 weeks showed a reduction in intraepithelial eosinophil counts ($p=0.005$) and substantial symptom improvement within 2-6 weeks (median 3 weeks)

Translated from English abstract. Article publicly available at [http://www.gastrojournal.org/article/0016-5085\(95\)90637-1/pdf](http://www.gastrojournal.org/article/0016-5085(95)90637-1/pdf)
AAF = amino acid-based formula; HPF = high-power (40x) field

Markowitz JE, Spergel JM, Ruchelli E, et al. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. Am J Gastroenterol. 2003;98:777-82

Background

Eosinophilic esophagitis (EoE) is an allergic gastrointestinal disease defined by the presence of a high concentration of eosinophils in the esophagus. Multiple management regimens for EoE have been reported, but with a lack of constancy in criteria used to define EoE and with variability in outcome measures. The aims of this research were to define a population of EoE patients with accuracy and to evaluate the effects of management with a strict amino acid-based diet.

Methods

In a 3-year period, patients who experienced chronic gastroesophageal reflux symptoms and an esophagogastroduodenoscopy (EGD) that revealed eosinophilic infiltration limited to the esophagus were included. They were managed with a proton pump inhibitor (PPI) for 3 months. Patients whose symptoms did not respond to PPI underwent follow-up studies to rule out or diagnose EoE. Those diagnosed with EoE were initiated on an amino acid-based formula (AAF) for 1 month, after which an EGD was repeated.

Results

A diagnosis of EoE was given to 14.7% (51/346) of subjects, who were ultimately enrolled in the intervention. Significant clinical improvement in gastrointestinal symptoms (emesis, gastralgia, and dysphagia) was seen within an average 8.5 days of initiating an AAF. An amino acid-based diet also resulted in significant histologic improvement, with before-diet esophageal eosinophils at a median of 33.7 per high-powered field, dropping to 1.0 following dietary intervention ($p < 0.01$).

Conclusion

In this group of pediatric patients diagnosed with EoE using well-defined criteria, following an amino acid-based diet led to dramatic improvement in both symptoms and histology.

Number of patients with symptoms pre- and post-management with amino acid-based formula (Neocate)

Symptoms	Before intervention	After 1 month on Neocate	P
Abdominal pain	40	2	<0.01
Vomiting	36	1	<0.01
Heartburn	27	2	<0.01
Water brash	11	1	<0.01
Globus	9	1	<0.01
Dysphagia	7	0	<0.01
Chest pain	4	0	0.04
Night cough	5	1	0.01
Irritability	3	0	0.08

Adapted from Markowitz et al. 2003

An amino acid-based diet (Neocate) was shown to significantly ($P < 0.01$) reduce symptoms within 8.5 days in this study of children and teenagers with EoE

Translated and adapted from English full text article - abstract publicly available at <http://www.ncbi.nlm.nih.gov/pubmed/12738455>

Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. Clin Gastroenterol Hepatol. 2005;3:1198-206

Background & Aims

Eosinophilic esophagitis (EoE) is a disorder characterized by a severe isolated eosinophilic infiltration of the esophagus unresponsive to aggressive acid blockade but responsive to the removal of dietary antigens. We present information relating to our 10-year experience in children diagnosed with EoE.

Methods

We conducted a retrospective study between January 1, 1994, and January 1, 2004, to evaluate all patients diagnosed with EoE. Clinical symptoms, demographic data, endoscopic findings, and the results of various treatment regimens were collected and evaluated.

Results

A total of 381 patients (66% male, age 9.1 +/- 3.1 years) were diagnosed with EoE: 312 presented with symptoms of gastroesophageal reflux (GER); 69 presented with dysphagia. Endoscopically, 68% of patients had a visually abnormal esophagus; 32% had a normal-appearing esophagus despite a severe histologic esophageal eosinophilia. The average number of esophageal eosinophils (per 400 x high power field) proximally and distally were 23.3 +/- 10.5 and 38.7 +/- 13.3, respectively. Corticosteroids significantly improved clinical symptoms and esophageal histology; however, upon their withdrawal, the symptoms and esophageal eosinophilia recurred. Dietary restriction or complete dietary elimination using an amino acid-based formula significantly improved both the clinical symptoms and esophageal histology in 75 and 172 patients, respectively.

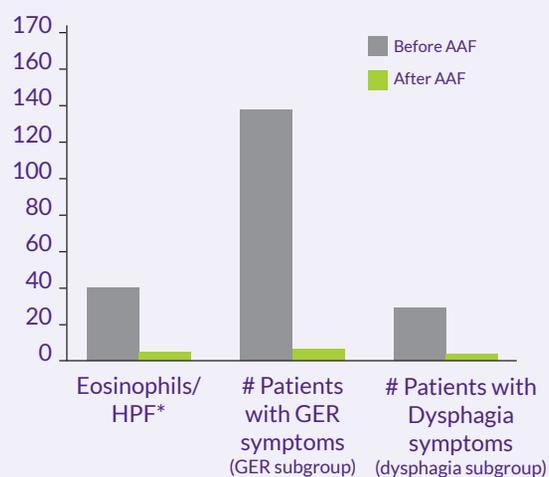
Removal of dietary antigens significantly improved clinical symptoms and esophageal histology in 98% of children with EoE – using an amino acid-based formula such as Neocate proved significantly better than selective food elimination at reducing eosinophils ($p < 0.05$)

Translated from English abstract. Article publicly available at [http://www.cghjournal.org/article/S1542-3565\(05\)00885-2/pdf](http://www.cghjournal.org/article/S1542-3565(05)00885-2/pdf)

Conclusions

Medications such as corticosteroids are effective; however, upon withdrawal, EoE recurs. The removal of dietary antigens significantly improved clinical symptoms and esophageal histology in 98% of patients.

Graph showing the impact of strict amino acid-based formula (AAF) on the number of esophageal eosinophils, GER and dysphagia for 164 patients



*High-power field

Adapted from Liacouras et al 2005

Rubenstein E, Lee JJ, Fred A, et al. Comparison of 2 delivery vehicles for viscous budesonide to treat eosinophilic esophagitis in children. J Pediatr Gastroenterol Nutr. 2014;59:317-20

Background:

For children with eosinophilic esophagitis (EoE), one management option is to mix Splenda® with budesonide to form a viscous solution for topical delivery, or oral viscous budesonide (OVB). However, many caregivers are hesitant to provide their children with large amounts of an artificial sweetener to deliver the steroid. This research asked if Neocate Nutra - a hypoallergenic semi-solid - as a delivery agent for OVB for children is at least as effective in managing EoE as Splenda.

Methods:

An approved review of medical records was performed retrospectively, seeking patients presenting to the Boston Children's Hospital Eosinophilic Gastrointestinal Disorder program and diagnosed with EoE. Sixty patients who chose management with an OVB were identified and categorized based on their choice to prepare OVB with Splenda (N=46) or with Neocate Nutra (N=14). Following a minimum of 10 weeks of OVB management, the primary outcome was the maximum number of eosinophils per high-power field (eos/HPF), with histologic response set at a threshold of <15eos/HPF.

Results:

Of patients managed with the Neocate Nutra/OVB slurry, 92.9% (13/14) showed histologic response (<15 eos/HPF), compared to 65% (30/46) of patients consuming the Splenda/OVB slurry. Examining mean pre- and post-management histology, the Neocate Nutra/OVB slurry group saw a decrease from 62 eos/HPF (20-120) to 9 eos/HPF (0-100). For the Splenda/OVB slurry group, the mean pre-management value was 59.5 eos/HPF (20-180), which dropped to 25.5 eos/HPF (0-200) post-management. Neocate Nutra was found to be noninferior to Splenda based on an odds ratio of success of 6.93 (95% CI 0.83-57.91, P=0.0728).

Conclusions:

In this noninferiority study, an OVB slurry prepared with Neocate Nutra for managing children with EoE was found to be at least as effective as the approach of preparing OVB with Splenda. For caregivers who prefer not to use the artificial sweetener called for in the standard recipe, Neocate Nutra represents an alternative OVB delivery agent that is palatable, novel and effective.

Neocate Nutra is an innovative, effective and palatable mixing agent to create a viscous budesonide slurry for the management of EoE

Translated and adapted from English full text article - publicly available at http://journals.lww.com/jpgn/Fulltext/2014/09000/Comparison_of_2_Delivery_Vehicles_for_Viscous.7.aspx

Splenda is a registered trademark of McNeil Nutritionals, LLC.

Warners MJ, Vlieg-Boerstra BJ, Verheij J, et al. Elemental diet decreases inflammation and improves symptoms in adult eosinophilic oesophagitis patients. *Aliment Pharmacol Ther.* 2017;45:777-87

Background

Eosinophilic esophagitis (EoE) is an unremitting disease driven by food allergens. EoE has been effectively managed by amino acid-based diets in children, but there is limited research on its effect in adults. Poor palatability of amino acid-based formula (AAF) is often cited as a primary reason for poor elemental diet adherence. This study examines the impact of managing EoE inflammation, symptoms and endoscopic findings in adults with EoE managed with a flavored liquid AAF (Neocate Splash).

Methods

This study prospectively included 21 adults with biopsy-confirmed EoE and reported symptoms of esophageal dysfunction. Subjects had a baseline and follow-up endoscopy after 4 weeks of an elimination diet with an AAF. Disease activity was assessed using peak eosinophilic count (eos/HPF) and visual endoscopic inspection. Questionnaires were used to evaluate symptoms and diet adherence. Serum levels of total IgE and total eosinophils were measured and inflammatory cytokine expression was analyzed.

Results

81% (17/21) of subjects completed the study and 71% (12/17) demonstrated complete histologic remission (≤ 15 eos/HPF) and 24% (4/17) showed partial histologic remission ($\geq 50\%$ reduction of pre-intervention eosinophil counts). The post-intervention average peak eosinophil count was significantly lower compared to pre-intervention average peak eosinophil count (40 vs. 9 eos/HPF; $P \leq 0.001$). Visual endoscopic signs of EoE markedly improved following diet. All 17 subjects reported significant decrease in symptoms, and 88% (15/17) were completely asymptomatic following diet intervention ($P \leq 0.001$). 82% (14/17) of subjects had a significant reduction of serum eosinophil counts and total IgE levels following intervention compared to baseline levels ($P \leq 0.05$).

Conclusion

In adult patients with eosinophilic esophagitis, an amino acid-based diet significantly decreased eosinophilic inflammation and induced histologic remission and symptom resolution.

17 adults with EoE successfully adhered to a 4-week elemental diet using flavored liquid AAF (Neocate Splash). Results revealed that these adults with EoE achieved significant improvement of esophageal inflammation, serum inflammatory markers and symptoms.

Warners MJ, Vlieg-Boerstra BJ, Verheij J, et al. Esophageal and small intestinal mucosal integrity in eosinophilic esophagitis and response to an elemental diet. Am J Gastroenterol. 2017:1-1

Background

Eosinophilic esophagitis (EoE) is characterized by impaired mucosal integrity and has been proposed to increase duodenal permeability. The removal of food allergens from the diet can restore esophageal mucosal integrity. This study evaluated duodenal permeability in EoE and assessed the impact of an elemental diet with an amino acid-based formula (AAF) on mucosal integrity of both the esophagus and duodenum.

Methods

This study prospectively evaluated 17 adults with EoE and included 8 reference healthy controls (HC). Biopsies of the esophagus were taken at baseline and following a 4-week diet of an AAF (Neocate Splash) – eosinophil counts and gene expression of proteins for barrier integrity and tight junctions were measured. Impedance of the esophagus and duodenum were measured using electrical tissue impedance spectroscopy and transepithelial resistance (TER) and transepithelial molecule flux were measured using Ussing chambers. A test for lactulose/mannitol (L/M) ratios was used to assess small intestinal permeability.

Results

In the EoE patients, mucosal integrity was impaired in the esophagus but not duodenum, as compared with HC. No significant differences were observed in L/M ratios between EoE patients and HC. Following AAF dietary intervention, histologic eosinophil counts decreased significantly, which was mirrored by normalizations of both esophageal impedance and transepithelial molecule flux. There was significant improvement in esophageal TER, but not to the levels observed in HC. Expression of genes that encode for filaggrin and desmoglein-1, barrier integrity proteins, was impaired in the esophagus at baseline but restored following AAF.

Conclusion

The use of an amino acid-based diet in adult EoE patients restores esophageal integrity, which suggests that food allergen exposure is at least partly responsible. Duodenal integrity does not seem to be affected in EoE, so may play a minor role in the pathophysiology of the disease.

This study showed that 4 weeks of dietary management of adults with EoE using an AAF (Neocate Splash) successfully restored esophageal integrity closer to that seen in healthy adults

Translated and adapted from publicly available English abstract - full text publicly available at <https://www.nature.com/ajg/journal/vaop/ncurrent/pdf/ajg2017107a.pdf>

Short Bowel Syndrome (SBS) in Infants and Children

Publication	Title	Study Purpose	Methodology	Result/Conclusion	Page number
Bines J et al. J Pediatr Gastroenterol Nutr. 1998;26:123-8.	Reducing parenteral requirements in children with short bowel syndrome: impact of an amino acid-based complete infant formula	To assess the impact of an AAF on enteral feeding tolerance and PN requirement in children with severe SBS	Children with SBS requiring PN since birth due to persistent feeding intolerances to eHF were assessed before and after using AAF (Neocate) for a follow-up period of 48 months	AAF (Neocate) eliminated the need for PN in patients with SBS who had previously required long-term PN	Abstract Page 35
Andorsky DJ et al. J Pediatr. 2001;139:27-33.	Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes	To determine correlates of clinical outcomes in patients with SBS	A retrospective review of neonates with SBS due to surgery, requiring ≥ 90 days of PN	Early enteral feeding with either breast milk or AAF after surgery (as well as length of small bowel) was associated with a shorter duration of PN and may influence intestinal adaptation	Abstract Page 36
De Greef E et al. J Nutr Metab. 2010;Volume 2010:1-6.	The influence of Neocate in paediatric short bowel syndrome on PN weaning	To describe the impact of the introduction of an amino acid based formula on PN weaning in four patients with short bowel syndrome	A retrospective case series of four patients with SBS who were weaned from PN after introduction of an AAF (Neocate)	SBS patients were able to wean PN and achieve enteral autonomy in a shorter time period compared to available literature, which may be due in part to the nonallergenic properties of Neocate	Abstract Page 37

AAF = amino acid-based formula; eHF = extensively hydrolyzed formula; PN = parenteral nutrition; SBS = short bowel syndrome.



Bines J, Francis D and Hill DJ. Reducing parenteral requirement in children with short bowel syndrome: impact of an amino acid-based complete infant formula. J Pediatr Gastroenterol Nutr. 1998;26:123-8

Background

The goal of parenteral nutrition for children with short bowel syndrome is to meet nutritional needs for growth and development while the intestine adapts to transition to enteral feedings in the future. However, not all patients are able to advance enteral feedings and many factors can affect feeding intolerance. This study of severe short bowel syndrome in children explores the influence of an amino acid-based infant formula on 1) tolerability of enteral nutrition and 2) the need for parenteral nutrition.

Methods

Children (n = 4) who required long-term parenteral nutrition following surgery that left them with severe short bowel syndrome (mean 45 cm small intestine) were enrolled. Subjects had been unable to advance enteral feeds due to gastrointestinal symptoms when being provided with an extensively hydrolyzed formula. Each was transitioned to a nutritionally complete amino acid-based formula - Neocate. They were monitored clinically for growth, feeding tolerance, biochemistry, stool analysis, food allergy testing, gastrointestinal biopsies, disaccharidase levels and intestinal permeability.

Results

All patients were able to discontinue parenteral nutrition within 15 months of starting Neocate, as vomiting resolved and stool output decreased in all patients within one month of starting Neocate. Jejunostomy output decreased from 53 mL/kg/day to 19 mL/kg/day in one patient and an average of 7 to 2.5 stools per day in the other 3 patients. Patient morbidity and hospitalization decreased in the 12 months after starting Neocate, dropping from an average hospitalization of 198 days in the year prior to Neocate use to 92 days/year after. After one year of Neocate, all patients remained on Neocate for the majority of their nutrition needs but were also able to incorporate oral food for 15-21% of total energy.

Conclusions

Within 15 months of starting Neocate, all four study patients were able to tolerate full enteral nutrition and discontinue long-term parenteral nutrition due to decreases in stool volume and output, resolution of vomiting and resolution of buttock excoriation. Clinical improvement was seen within one month of the study formula and was accompanied by improvement in measurements of intestinal function.

Feeding an AAF (Neocate) improved feeding tolerance and eliminated chronic reliance on parenteral nutrition in children with severe SBS

Translated and adapted from English full text article - publicly available at http://journals.lww.com/jpgn/Fulltext/1998/02000/Reducing_Parenteral_Requirement_in_Children_with.1.aspx

Andorsky DJ, Lund DP, Lillehei CW, et al. Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. J Pediatr. 2001;139:27-33

Objective

To determine correlates of clinical outcomes in patients with short bowel syndrome (SBS).

Methods

Retrospective medical record review of neonates treated between 1986 and 1998 who met our criteria for SBS: dependence on parenteral nutrition (PN) for at least 90 days after surgical therapy for congenital or acquired intestinal diseases.

Results

Thirty subjects with complete data were identified; 13 (43%) had necrotizing enterocolitis, and 17 (57%) had intestinal malformations. Mean (SD) residual small bowel length was 83 (67) cm. Enteral feeding with breastmilk ($r = -0.821$) or an amino acid-based formula ($r = -0.793$) was associated with a shorter duration of PN, as were longer residual small bowel length ($r = -0.475$) and percentage of calories received enterally at 6 weeks after surgery ($r = -0.527$). Shorter time without diverting ileostomy or colostomy ($r = 0.400$), enteral feeding with a protein hydrolysate formula ($r = -0.476$), and percentage of calories received enterally at 6 weeks after surgery ($r = -0.504$) were associated with a lower peak direct bilirubin concentration. Presence of an intact ileocecal valve and frequency of catheter-related infections were not significantly correlated with duration of PN. In multivariate analysis, only residual small bowel length was a significant independent predictor of duration of PN, and only less time with a diverting ostomy was an independent predictor of peak direct bilirubin concentration.

Conclusions

Although residual small bowel length remains an important predictor of duration of PN use in infants with SBS, other factors, such as use of breast milk or amino acid-based formula, may also play a role in intestinal adaptation. In addition, prompt restoration of intestinal continuity is associated with lowered risk of cholestatic liver disease. Early enteral feeding after surgery is associated both with reduced duration of PN and less cholestasis.

Enteral feeding with breast milk or an AAF (Neocate) was associated with a shorter duration of parenteral nutrition in neonates with SBS, and may influence intestinal adaptation

Translated from English abstract - available at [https://www.jpeds.com/article/S0022-3476\(01\)85158-1/fulltext](https://www.jpeds.com/article/S0022-3476(01)85158-1/fulltext)

De Greef E, Mahler T, Janssen A, et al. The influence of Neocate in paediatric short bowel syndrome on PN weaning. J Nutr Metab. 2010;Volume 2010:1-6

Clinical management of short bowel syndrome remains a multistage process. Although PN is crucial, early introduction of enteral feeding is mandatory. We describe retrospectively 4 patients with an ultrashort bowel who could be weaned off PN on very short terms after introduction of an amino-acid-based formula (Neocate).

Patient 1 had congenital short bowel with 50 cm small bowel and 30 cm colon. He had persistent diarrhoea on a semielementary formula. When Neocate was introduced he could be weaned from PN within 6 months. Patient 2 needed multiple surgical interventions because of NEC at D 27. He maintained 40 cm small bowel and an intact colon and remained PN dependent on semielemental formula. After introducing Neocate, PN could be weaned within 3 months.

In the next 2 patients, Neocate was introduced as initial enteral feeding after bowel resection following antenatal midgut volvulus. Patient 3 had 20 cm small bowel and an intact colon. PN was weaned after 2 months. Patient 4 had 9 cm small bowel and an intact colon. PN was weaned after 13 months. In all patients ileocaecal valve (ICV) was preserved.

No consensus is reached on the type of formula to use for short bowel syndrome. Compared to recent data in the literature, the weaning period in these 4 patients was significantly shortened on an amino acid based formula. The reason for this may lie in the antiallergic properties of this formula.

We recommend the use of an amino-acid-based formula to induce earlier weaning of PN.

The use of an amino acid-based formula (Neocate) in SBS infants may support earlier weaning of PN, minimizing costs and complications

Translated from English abstract - article publicly available at <https://www.ncbi.nlm.nih.gov/pmc/PMC2915748>

Other Gastrointestinal (GI) conditions related to food allergies

Publication	Title	Study Purpose	Methodology	Result/Conclusion	Page number
Estep DC et al. Acta Paediatr. 2000;89:22-7.	Treatment of infant colic with amino acid-based infant formula: a preliminary study	To examine whether an AAF would be accepted in infants with colic and whether it would improve their symptoms	Infants with colic behavior (confirmed by diaries) were assessed for symptom improvement following exclusive feeding with an AAF (Neocate) for 5-17 days	Infants with colic behavior tolerated an AAF with symptom improvement within 1-2 days. Time spent crying and fussing was reduced by 45% in these infants	Abstract Page 39

AAF = amino acid-based formula



Estep DC, Kulczycki A, Jr. Treatment of infant colic with amino acid-based infant formula: a preliminary study. Acta Paediatr. 2000;89:22-7

Background

Colic is common in infants, and has been commonly defined as episodes of fussing and/or crying exceeding 3 hours a day and more than 3 days per week. Research suggests cow milk protein seems to contribute to colic in a large fraction of infants, with disagreement on the potential effectiveness of casein hydrolysates. This trial examined the acceptance of the amino acid-based infant formula Neocate by infants with colic and the impact of Neocate on colic symptoms.

Methods

Six formula-fed infants (aged 3-7 weeks) were studied using Barr-type infant behavior diaries to assess cry time, fuss time and sleep for 3-6 days on their current formula, and again following a switch to an exclusive diet of Neocate for 5-17 days. At the end of the intervention period following symptom improvement, infants were orally challenged with bovine IgG (BGG).

Results

All infants accepted and tolerated Neocate well and improved, with the majority having decreases in cry time and fuss time within one or two days of switching to Neocate. Cry + fuss time decreased compared to baseline at days 2-5 ($p \leq 0.02$) and days 6-10 ($p \leq 0.002$). Daily combined cry and fuss time decreased an average of 148 minutes per day (45%). Oral BGG exposure led to increased "cry time" and fussing, indicating a potential role for the protein in the etiology of infant colic.

Conclusion

Neocate was well tolerated by infants with colic, with rapid reductions in crying and fussing. The observed benefits of an amino acid-based formula, and increase in symptoms with BGG challenge, are consistent with the hypothesis that proteins/peptides in cow milk may contribute to colic.

Feeding an AAF (Neocate) in infants with colic related to milk allergy is well tolerated, showing a "striking improvement" in crying and fussing times (within 1 to 2 days) in these infants

Translated and adapted from English full text article - abstract publicly available at <http://www.ncbi.nlm.nih.gov/pubmed/10677052>



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