

THE SCIENCE OF SYNBIOTICS IN COW'S MILK ALLERGY MANAGEMENT

INTRODUCTION

Breast milk is the best possible nutrition for infants – it contains everything they need for healthy growth and development. However, it may not always be possible for all CMA infants. Therefore, healthcare professionals may prescribe specialized hypoallergenic formulas for dietary management.

Synbiotics are the latest addition to our range of hypoallergenic formula for infants with cow's milk allergy (CMA). This blend of synbiotics contains our unique mix of prebiotics and probiotics that work together synergistically to support the gut microbiota and developing immune system, and is backed by 10 years of research in 1,500 infants.

In addition to effective symptom resolution and proven hypoallergenicity, three clinical studies show that our hypoallergenic formulas with synbiotics positively influence the gut microbiota of cows' milk allergic infants bringing it closer to that of healthy breastfed infants, to support the developing immune system (Figure 1)¹⁻⁴.

Now additional outcomes show fewer reports of antibiotic use, infections, and hospitalizations due to infections based on evaluation of adverse events in studies with AAF with synbiotics¹⁻⁴.

This booklet contains the clinical abstracts presenting the latest scientific evidence supporting the role of hypoallergenic formula with synbiotics in the dietary management of CMA.

Figure 1:

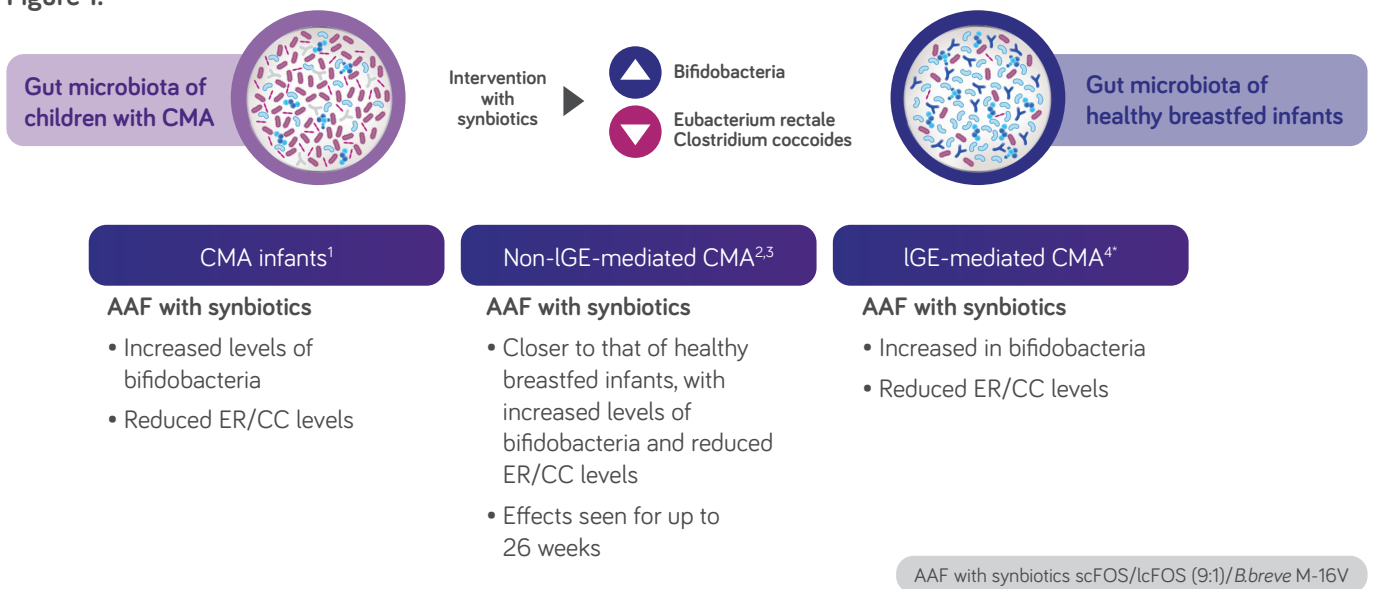


Figure 1: Three randomised controlled trials demonstrated that synbiotics rebalance the gut microbiota in infants with cow's milk allergy and bring it closer to that of healthy breastfed infants.

*PRESTO, unpublished data.

AAF: amino acid-based formula; B. brevue M-16V: *Bifidobacterium breve* M-16V; CC: *Clostridium coccooides*; CMA: cow's milk allergy; ER: *Eubacterium rectale*; lcFOS: long-chain fructo-oligosaccharides; scFOS: short-chain fructo-oligosaccharides.

Adapted from Burks et al., Candy et al., and Fox et al.

REFERENCES

- Burks A et al. *Pediatr Allergy Immunol.* 2015;26(4):316-22.
- Candy D et al. *Pediatr Res.* 2018;83(3):677-86.
- Fox AT et al. *Clin Transl Allergy.* 2019;9:5.
- Chatchatee P et al. *EAACI Media Library* 2019.

SYNBIOTICS-SUPPLEMENTED AMINO ACID-BASED FORMULA SUPPORTS ADEQUATE GROWTH IN COW'S MILK ALLERGIC INFANTS

Burks A *et al.* *Pediatr Allergy Immunol.* 2015;26(4):316-22.

BACKGROUND

Children with cows' milk allergy (CMA) are at risk for inadequate nutritional intake and growth. Dietary management of CMA, therefore, requires diets that are not only hypoallergenic but also support adequate growth in this population. This study assessed growth of CMA infants when using a new amino acid-based formula (AAF) with prebiotics and probiotics (synbiotics) and evaluated its safety in the intended population.

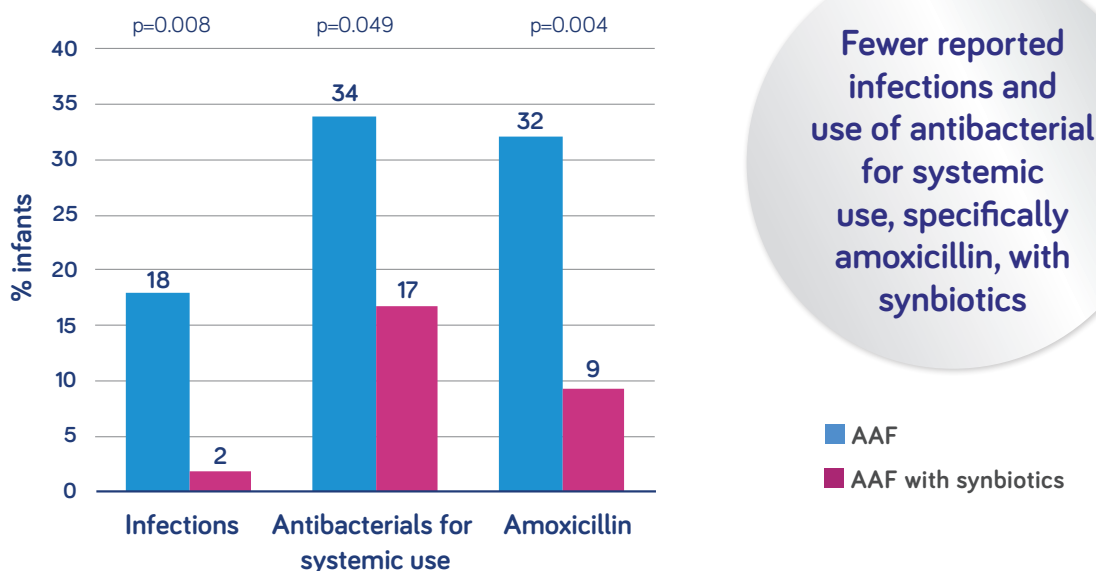
METHODS

In a prospective, randomized, double-blind controlled study, full-term infants with diagnosed CMA received either an AAF (control; n=56) or AAF with synbiotics (oligofructose, long-chain inulin, acidic oligosaccharides, *Bifidobacterium breve* M-16V) (test; n=54) for 16 wk. Primary outcome was growth, measured as weight, length and head circumference. Secondary outcomes included allergic symptoms and stool characteristics.

RESULTS

Average age +/- (SD) of infants at inclusion was 4.5 +/- 2.4 months. Both formulas equally supported growth according to WHO 2006 growth charts and resulted in similar increases of weight, length and head circumference. At week 16, differences (90% CI) in z-scores (test-control) were as follows: weight 0.147 (-0.10; 0.39, p=0.32), length -0.299 (-0.69; 0.09, p=0.21) and head circumference 0.152 (-0.15; 0.45, p=0.40). Weight-for-age and length-for-age z-scores were not significantly different between the test and control groups. Both formulas were well tolerated and reduced allergic symptoms; the number of adverse events was not different between the groups.

ADVERSE EVENTS AND MEDICATION USAGE[†]



[†]Exploratory findings do not intend to offer final and conclusive results. Further research is needed to confirm the findings.

CONCLUSIONS

This is the first study that shows that an AAF with a specific synbiotic blend, suitable for CMA infants, supports normal growth and growth similar to the AAF without synbiotics. Also observed were significantly fewer infections and lower use of antibacterials for systemic use (antibiotics) reported as adverse events and medication usage.

A SYNBIOTIC-CONTAINING AMINO-ACID-BASED FORMULA IMPROVES GUT MICROBIOTA IN NON-IgE-MEDIATED ALLERGIC INFANTS

Candy D *et al.* *Pediatr Res.* 2018;83(3):677-86.

BACKGROUND

Prebiotics and probiotics (synbiotics) can modify gut microbiota and have potential in allergy management when combined with amino acid-based formula (AAF) for infants with cows' milk allergy (CMA).

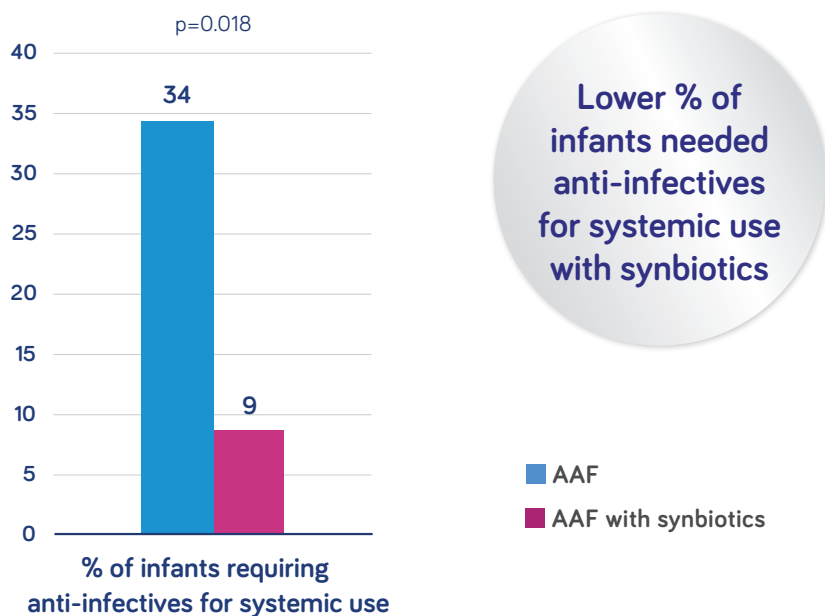
METHODS

This multicenter, double-blind, randomized controlled trial investigated the effects of an AAF-including synbiotic blend on percentages of bifidobacteria and *Eubacterium rectale/Clostridium coccoides* group (ER/CC) in feces from infants with suspected non-IgE-mediated CMA. Feces from age-matched healthy breastfed infants were used as reference (healthy breastfed reference (HBR)) for primary outcomes. The CMA subjects were randomized and received test or control formula for 8 weeks. Test formula was a hypoallergenic, nutritionally complete AAF including a prebiotics blend of fructooligosaccharides and the probiotic strain *Bifidobacterium breve* M-16V. Control formula was AAF without synbiotics.

RESULTS

A total of 35 (test) and 36 (control) subjects were randomized; HBR included 51 infants. At week 8, the median percentage of bifidobacteria was higher in the test group than in the control group (35.4% vs. 9.7%, respectively; $p < 0.001$), whereas ER/CC was lower (9.5% vs. 24.2%, respectively; $p < 0.001$). HBR levels of bifidobacteria and ER/CC were 55% and 6.5%, respectively.

ADVERSE EVENTS AND MEDICATION USAGE[†]



CONCLUSIONS

AAF including specific synbiotics, which results in levels of bifidobacteria and ER/CC approximating levels in the HBR group, improves the fecal microbiota of infants with suspected non-IgE-mediated CMA. Furthermore, analysis of medication usage showed that a significantly lower percentage of infants in the test group needed anti-infectives for systemic use.

A SPECIFIC SYNBIOTIC-CONTAINING AMINO ACID-BASED FORMULA IN DIETARY MANAGEMENT OF COW MILK ALLERGY: A RANDOMIZED CONTROLLED TRIAL

Fox AT *et al.* Clin Transl Allergy. 2019;9:5.

BACKGROUND

Here we report follow-up data from a multicenter, double-blind, randomized, controlled trial, which investigated fecal microbiota changes with a new amino acid-based formula (AAF) including synbiotics in infants with non-IgE-mediated cows' milk allergy (CMA).

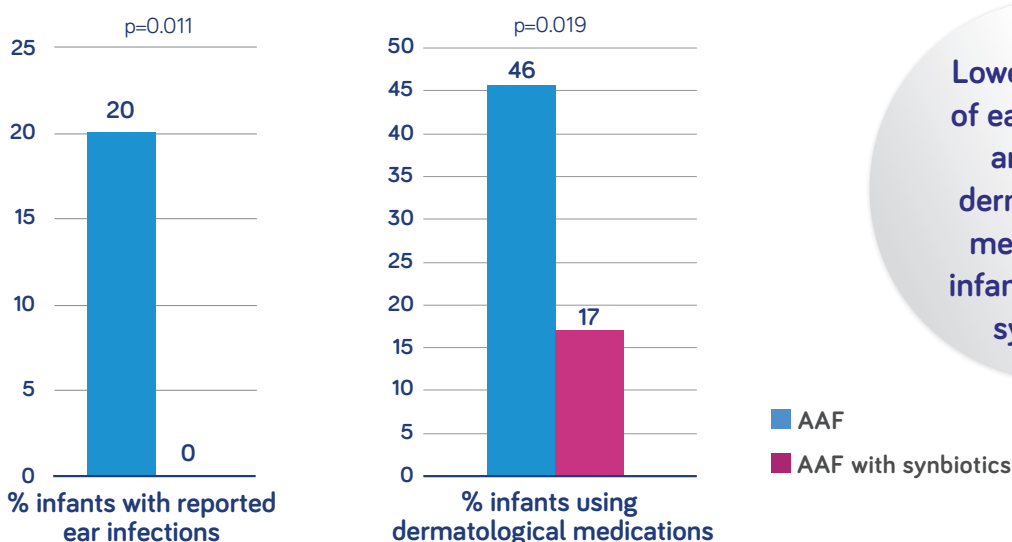
METHODS

Subjects were randomized to receive test product (AAF including fructooligosaccharides and *Bifidobacterium breve* M-16V) or control product (AAF) for 8 weeks, after which infants could continue study product until 26 weeks. Fecal percentages of bifidobacteria and *Eubacterium rectale/Clostridium coccooides* group (ER/CC) were assessed at 0, 8, 12, and 26 weeks. Additional endpoints included stool markers of gut immune status, clinical symptoms, and safety assessments including adverse events and medication use.

RESULTS

The trial included 35 test subjects, 36 controls, and 51 in the healthy reference group. Study product was continued by 86% and 92% of test and control subjects between week 8–12, and by 71% and 80%, respectively until week 26. At week 26, median percentages of bifidobacteria were significantly higher in test than control [47.0% vs. 11.8% ($p < 0.001$)], whereas percentages of ER/CC were significantly lower [(13.7% vs. 23.6% ($p = 0.003$))]. Safety parameters were similar between groups. Interestingly, use of dermatological medication and reported ear infections were lower in test versus control, $p = 0.019$ and 0.011 , respectively[†]. Baseline clinical symptoms and stool markers were mild (but persistent) and low, respectively. Symptoms reduced towards lowest score in both groups.

ADVERSE EVENTS AND MEDICATION USAGE[†]



[†]Exploratory findings do not intend to offer final and conclusive results. Further research is needed to confirm the findings.

CONCLUSIONS

Beneficial effects of this AAF including specific synbiotics on microbiota composition were observed over 26 weeks, and shown suitable for dietary management of infants with non-IgE-mediated CMA. Furthermore, analysis of adverse events and medication usage showed significantly lower use of dermatological medication and a lower incidence of ear infections for infants in the test group.

TOLERANCE DEVELOPMENT IN INFANTS WITH IgE-MEDIATED COW'S MILK ALLERGY RECEIVING AMINO ACID-BASED FORMULA INCLUDING SPECIFIC SYNBIOTICS: A MULTI-CENTER RANDOMIZED CONTROLLED CLINICAL TRIAL (PRESTO)

Chatchatee P *et al.* EAACI Media Library 2019. Abstract presented at EAACI PAAM. Florence, Italy, October 2019.

BACKGROUND

Cow's milk allergy (CMA) is the most common food allergy in infancy and may persist into later life. CMA may be managed with a hypoallergenic amino acid-based formula (AAF), where breastfeeding is not possible. Here we report the data from a multi-center prospective, randomized, double-blind controlled clinical study aimed to evaluate development of cow's milk (CM) tolerance, allergy symptoms and safety of an AAF including synbiotics in infants with confirmed IgE-mediated CMA.

METHODS

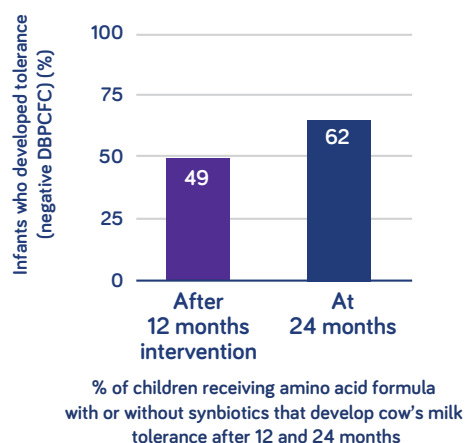
Subjects were randomized to receive either AAF including synbiotics (test product) or AAF (control product) for 12 months. Stratification was based on CM skin prick test wheal size and study site. After 12 months subjects followed diet as advised by clinician. At 12 and 24 months, CM tolerance was evaluated by double-blind placebo-controlled food challenge. At baseline, 6, 12, and 24 months, symptoms were recorded via clinician reports and parent diaries. Adverse events (AE) and concomitant medication were monitored. Data was analyzed based on the all subjects randomized data set using a logistic regression model.

RESULTS

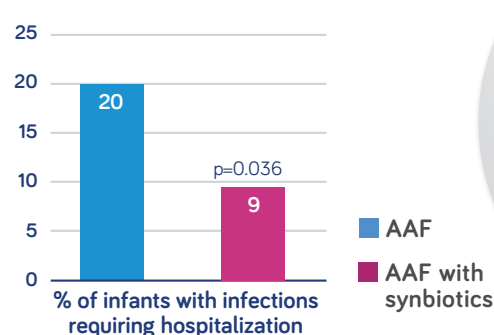
At baseline, mean age (\pm SD) of CMA infants ($n=169$) was 9.4 ± 2.5 months, 72% male, 50% born via caesarean section. Eczema (66%) and urticaria (22%) were at study entry reported as the most frequent predominant symptom.

After 12-months intervention, 49% of subjects developed CM tolerance: 45% in test group and 52% in control; $p=0.401$. At 24 months 62% developed CM tolerance: 64% in test and 59% in control group; $p=0.530$. During the 12-months intervention, significantly fewer infants in the test group (8.8%) required hospitalization due to serious AE categorized as infections compared to the control group (20.2%; $p=0.036$).

TOLERANCE DEVELOPMENT



SERIOUS ADVERSE EVENTS[†]



Approximately 50% of children receiving an AAF developed tolerance after 12 months and significantly fewer infants required hospitalization due to infections

[†]Exploratory findings do not intend to offer final and conclusive results. Further research is needed to confirm the findings.

CONCLUSIONS

This is the first study that shows that tolerance development on an AAF is in line with what has been reported previously in infants with IgE-mediated CMA who achieved natural tolerance to cow's milk after 12-18 months. Among infants receiving an AAF including or excluding synbiotics, 49% developed CM tolerance at 12 months and 62% at 24 months with no statistically significant differences observed between the groups. During the 12-months intervention significantly fewer infants receiving AAF including synbiotics required hospitalization due to infections.

