Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

COURSE TRANSCRIPT

Reducing Allergic Manifestations in Children with Cow's Milk Allergy: Current Research

Overview

Prof. Roberto Berni Canani, MD, PhD, presents data from a trial of infants with cow's milk allergy (CMA). In Dr. Canani's trial, allergic manifestations during a 36-month trial of extensively hydrolyzed formula, with or without Lactobacillus rhamnosus GG, were determined in infants who had developed CMA between 1-12 months of age. Dr. Canani's research has implications for the treatment of cow's milk intolerance, and long-term outcomes for children who develop CMA, since substitutive formulas can be used to treat these patients.

Target Audience

This activity was developed for pediatric physicians, nurses, nurse practitioners, dietitians, allergists and other health care providers who have an interest in newborns, infants and toddlers.

Learning Objectives

At the conclusion of these activities, participants should be better able to:

- Identify the long-term risks associated with cow's milk allergy early in life
- Mediate allergic manifestations in infants by applying a probiotic nutritional strategy

Faculty

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Roberto Berni Canani, MD, PhD

Research Support Mead Johnson Nutrition

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Additional content planners

Anna Nowak-Wegrzyn, MD (peer reviewer)

Research Support Astellas–clinical area: peanut vaccine phase I clinical trial
DBV Technologies–clinical area: peanut and milk patch immunotherapy Phase III clinical trials
Nestlé–clinical area: hypoallergenicity of the new infant formula-trial
Nutricia–clinical area: hypoallergenicity of the new infant formula-trial
Thermo Fisher Scientific–clinical area: molecular diagnostics

The following have no significant relationship to disclose:
Chris Fischer (medical writer)
Gabrielle Schwilk, FNP-BC, MSN (lead nurse planner)

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This activity is supported by an independent educational grant from **Mead Johnson Nutrition**.

Reducing Allergic Manifestations in Children with Cow's Milk Allergy: Current Research

This activity is an online enduring material. Successful completion is achieved by reading and/or viewing the materials, reflecting on its implications in your practice, and completing the assessment component.

The estimated time to complete the activity is 1.0 hour.

This activity was released on April 1, 2017 and is eligible for credit through March 31, 2019.

Contact Information

For help or questions about this activity please contact Continuing Education:

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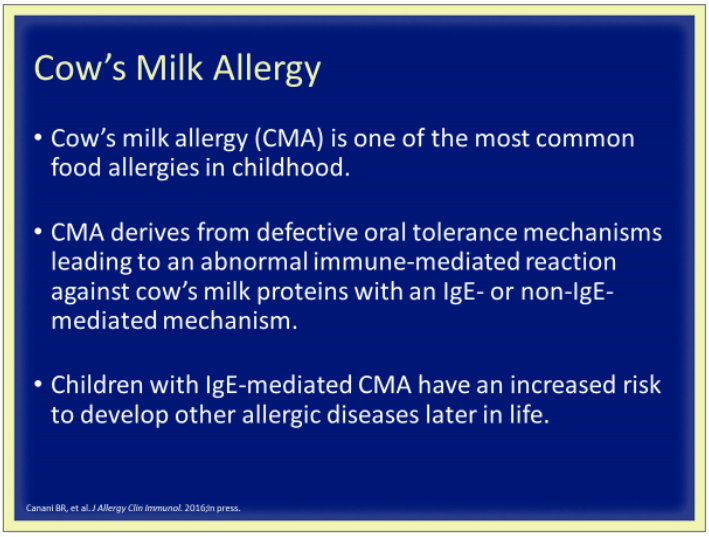
Editor's Note: This is a transcript of a live presentation on February 28, 2017.

Dr. Roberto Berni Canani: I'm Roberto Berni Canani and today I am pleased to present our most recent research results on a relevant problem for the pediatric age, cow milk allergy.

Worldwide, cow milk allergy is one of the most common food allergies in childhood. The prevalence and severity of the clinical manifestation of cow milk allergy increased at an alarming rate in the last years. In Italy, in my country, in the last 10 years, we observed a 500% increase in the number of children requiring hospitalization for cow milk protein-induced anaphylactic reactions.



Slide 1

Cow milk allergy derives from a defective oral tolerance mechanism leading to an abnormal immune-mediated reaction against cow milk proteins, which in turn could induce an IgE-mediated or a non-IgE-mediated mechanism. Another important aspect is that cow milk allergy is now recognized as the first indicator of a dysregulation of the immune system in children. In fact, babies with cow milk allergy have an increased risk to develop other allergic diseases later in life, the so-called atopic march.

The first line of treatment for all children affected by food allergy is the elimination diet, but the peculiarity of cow milk allergy is that, in this condition, we can use different formulas, including extensively hydrolyzed casein or whey formulas, soy- or rice-based formulas or amino-acid-based formula. We recently showed that in children with cow milk allergy, the use of a normative dietary strategy, based on extensively hydrolyzed casein formula supplemented with probiotic LGG, is able to induce a faster acquisition of immune tolerance.

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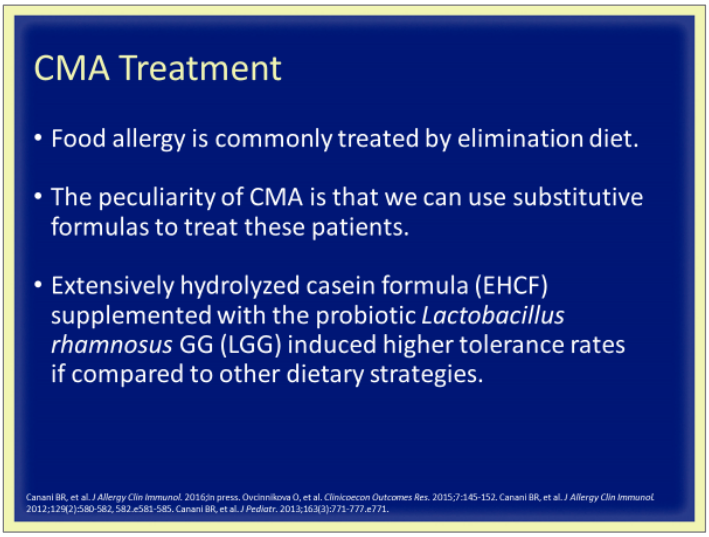

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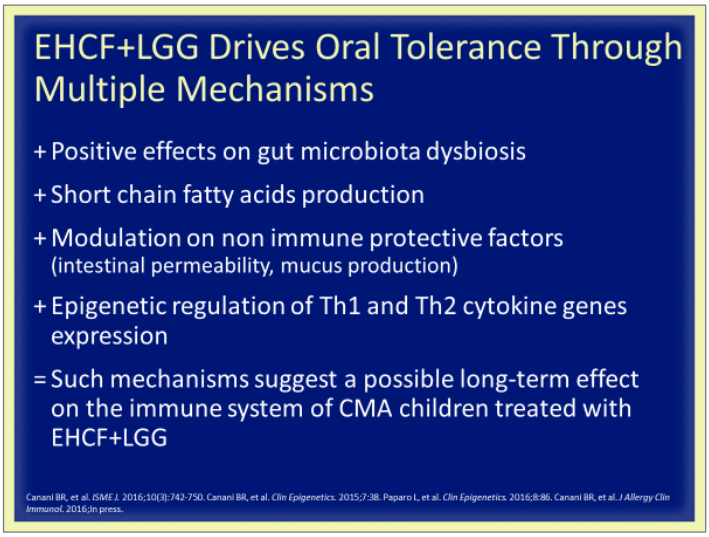

Slide 3

In recent years, together with other research groups in Europe and the United States, we have focused on the mechanism of action of this novel dietary strategy. Preliminary data suggests that this dietary strategy exhibits positive effects on gut microbiota composition, short chain fatty acid productions, in particular butyrate, a very important short chain fatty acid that exerts many effects at the immune system level, in particular driving epigenetic modification of the mechanism of immune tolerance and a well-tuned epigenetic regulation of gene involving allergic response. Such mechanisms suggest a possible long-term effect elicited by this new dietary strategy on the immune system of a child affected by cow milk allergy.

So, our most recent research activity was focused to test whether this normative dietary strategy, based on extensively hydrolyzed casein formula supplemented with the probiotic LGG, could influence the occurrence of other allergic manifestation in children affected by cow milk allergy. And we evaluated IgE-mediated cow milk allergy patients because these subjects are at increasing risk to develop other atopic manifestations.

We designed a randomized, controlled trial. The primary outcome of the study was the occurrence of any atopic manifestation during a 3-years follow-up, in particular eczema, urticaria, asthma and rhinoconjunctivitis. The secondary outcome was the acquisition of immune tolerance after 1 year, 2 years and 3 years of dietary treatment.

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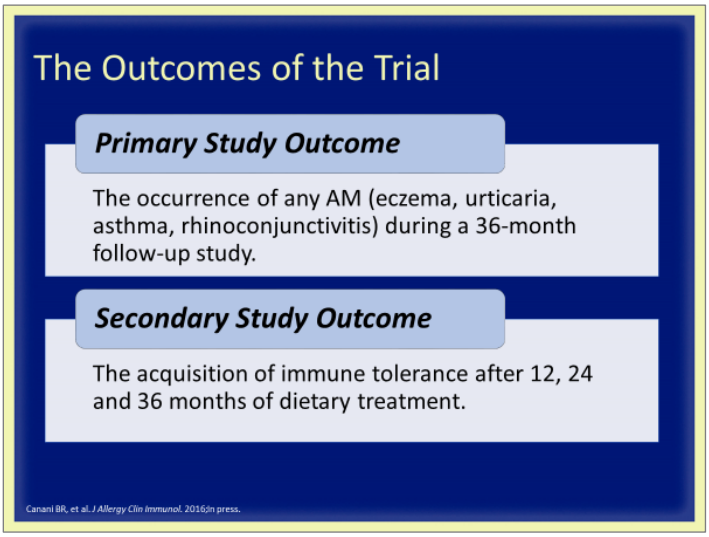
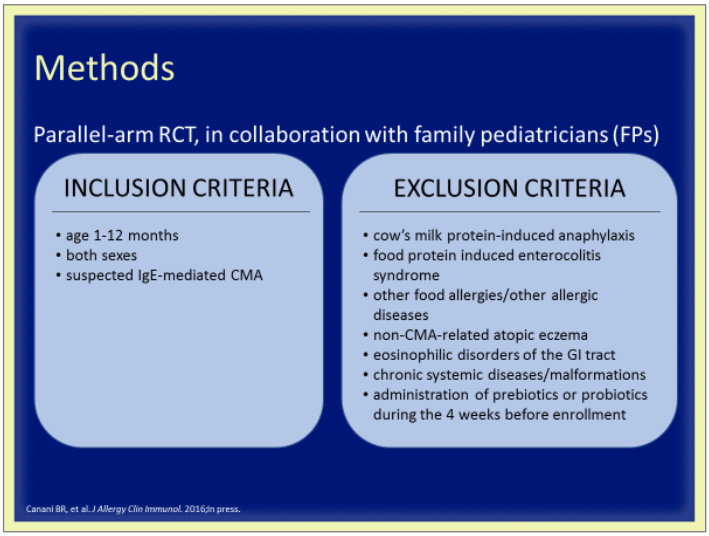


Slide 4

The parallel-arm randomized, controlled trial was designed to test whether hydrolyzed casein formula supplemented with probiotic LGG, can reduce the incidence of other allergic manifestations, compared to a hydrolyzed casein formula not containing the probiotic, in children with IgE-mediated cow milk allergy.

The trial was performed in collaboration with family pediatricians who care for children up to the age of 14 years in the Italian national health system.

Before starting the study, all involved family pediatricians attended an investigator meeting where the study protocol was illustrated and discussed and all the procedures and definitions were shared. The inclusion criteria were age—between one month to 12 months—and suspected IgE-mediated cow milk allergy. The exclusion criteria were cow milk protein-induced anaphylaxis, food protein-induced enterocolitis syndrome and other food allergies, other allergic diseases, no cow milk allergy-related atopic eczema, eosinophilic disorders of the gastrointestinal tract, chronic systemic diseases, congenital cardiac defects, active tuberculosis, autoimmune diseases, immunodeficiency, chronic inflammatory bowel diseases, celiac disease, cystic fibrosis, metabolic diseases, malignancy and chronic pulmonary diseases and malformation of the gastrointestinal and/or respiratory tract, and administration of prebiotics or probiotics during the 4 weeks before enrollment. Only subjects who met the inclusion criteria were invited to participate in the study.



Slide 5

Anamnestic, demographic, anthropometric and clinical data, as well as information on socioeconomic factors, family and living conditions, parental history of allergic diseases, maternal smoking during pregnancy, environmental tobacco smoke exposure and number of siblings, and pet ownership, were obtained from the parents of each infant and recorded in a specific clinical database.

Then, we performed skin prick tests and, according to a randomization list prepared by a biostatistician who was not involved in the statistical analysis, infants were randomly allocated to one of the 2 groups of dietary intervention. Group 1 received extensively hydrolyzed casein formula alone, and group 2 received extensively hydrolyzed casein formula containing the probiotic LGG.

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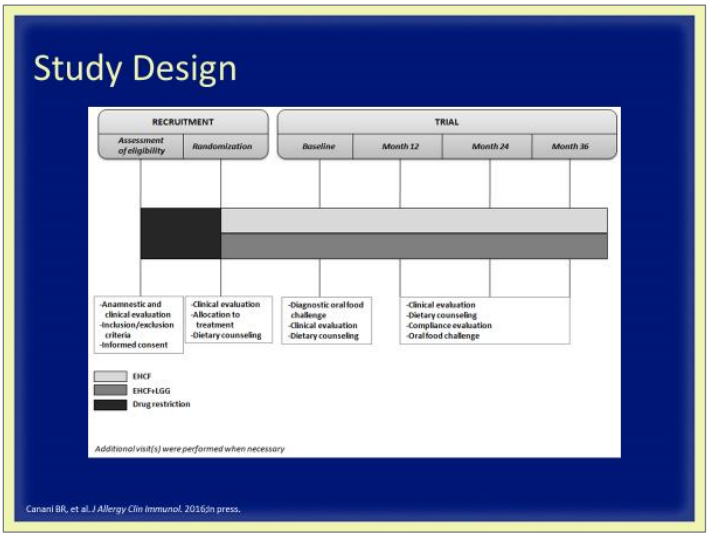
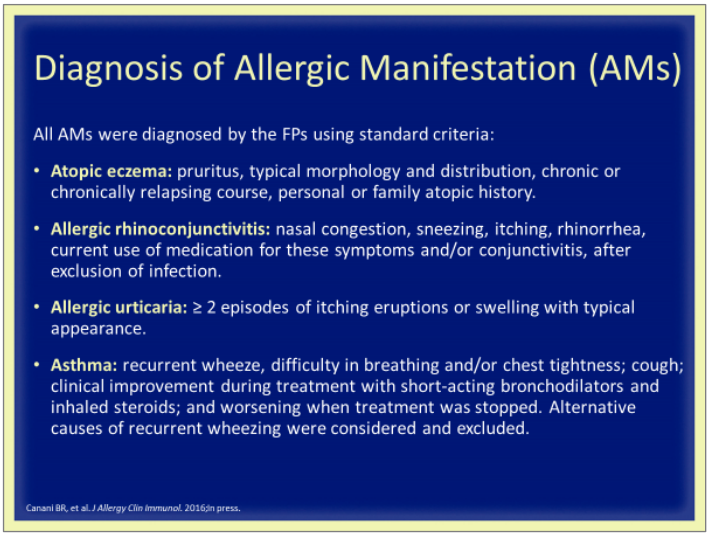


Slide 6

From 2 weeks to 4 weeks after the first assessment, when a full and stable remission of cow milk allergy symptoms was achieved, a double-blind, placebo-controlled food challenge was performed. The recruitment of children continued until a prespecified number of 110 subjects per group with cow milk allergy was achieved, and only these subjects continued the exclusion diet using the hypoallergenic formula prescribed at randomization and started the trial.

Then, during a 3-year follow-up, at least 3 visits—at 12 months, at 24 months and 36 months—after the start of the study, were performed. Skin prick tests and oral food challenges were performed to explore tolerance acquisition to cow milk every one year and clinical tolerance acquisition was defined by the presence of a negative oral food challenge. Children with a negative oral food challenge at any subsequent visit were reevaluated after 6 months to check for the persistence of oral tolerance acquisition. Only children with negative food challenge at any follow-up stopped the consumption of the study formula.

Unscheduled visits were made when the family pediatrician noticed any allergic symptoms. At each visit, the children were examined by the family pediatrician, body growth was assessed and a structured interview on health problems, including allergic symptoms, was carried out. All diagnoses of other allergic manifestations were performed by a tertiary center by 2 investigators blinded to the group assignment. In the case of discordance about an atopic manifestation diagnosis, further evaluation by a third pediatrician, experienced in pediatric allergy, was performed.



Slide 7

Clinical tolerance acquisition was defined by the presence of a negative oral food challenge and children with a negative oral food challenge at any subsequent visit were reevaluated to check for the persistence of oral tolerance acquisition. Only children with negative oral food challenge at any follow-up stopped the consumption of study formula.

As you can see here [Slide 7], all allergic manifestations were diagnosed by the family pediatrician using standardized criteria.

This is the flow of subjects during the study [Slide 8]. Because children had to have a double-blind, placebo-controlled food challenge-confirmed

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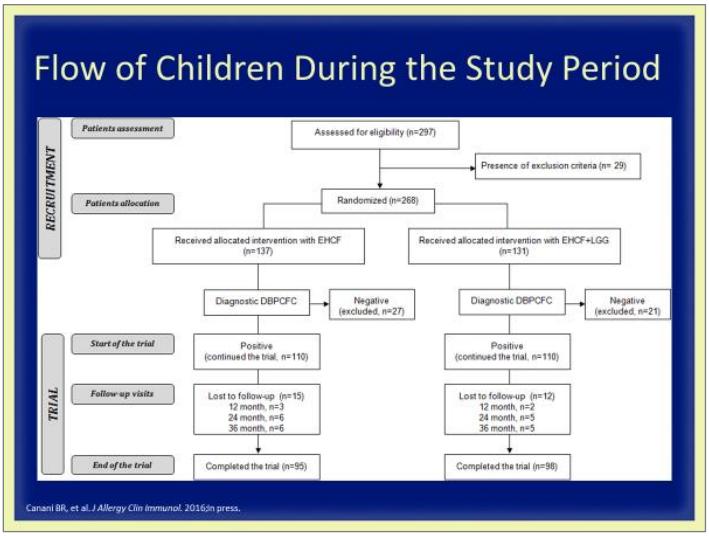
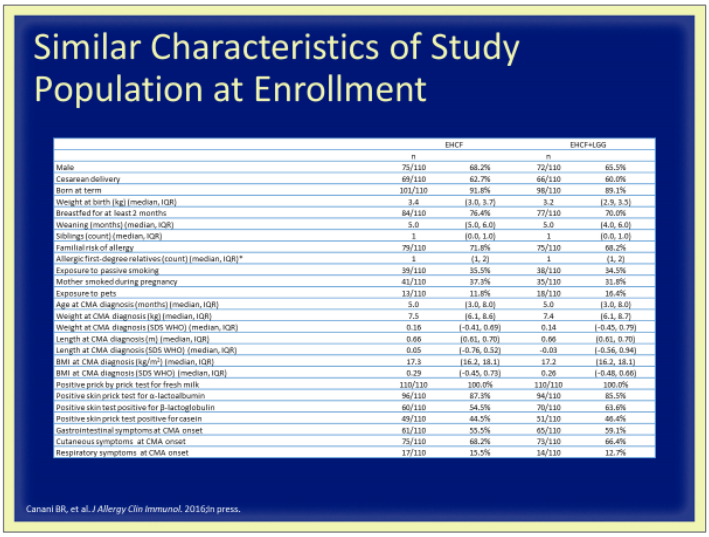
diagnosis of cow milk allergy, we increased the pool of children allocated to the treatments and we designed the study to enroll up to 150 children per group until at least 110 children per group in a double-blind, placebo-controlled, food challenge-confirmed diagnosis of cow milk allergy. A total of 27 children were lost during the follow-up, 15 in one group and 12 in the extensively hydrolyzed casein formula supplemented with the LGG group.



Slide 8

These are the main demographic and clinical features of the study population. As you can see here [Slide 9], at the baseline, all main features of the study groups were similar. All children were from families of middle socioeconomic status and lived in urban areas.



	EHCF		EHCF+LGG	
	n		n	
Male	75/110	68.2%	72/110	65.5%
Cesarean delivery	69/110	62.7%	66/110	60.0%
Born at term	101/110	91.8%	98/110	89.1%
Weight at birth (kg) (median, IQR)	3.4	(3.0, 3.7)	3.2	(2.9, 3.5)
Breastfed for at least 2 months	84/110	76.4%	77/110	70.0%
Weaning (months) (median, IQR)	5.0	(5.0, 6.0)	5.0	(4.0, 6.0)
Siblings (count) (median, IQR)	1	(0.0, 1.0)	1	(0.0, 1.0)
Familial risk of allergy	79/110	71.8%	75/110	68.2%
Allergic first-degree relatives (count) (median, IQR)*	1	(1, 2)	1	(1, 2)
Exposure to passive smoking	39/110	35.5%	38/110	34.5%
Mother smoked during pregnancy	41/110	37.3%	35/110	31.8%
Exposure to pets	13/110	11.8%	18/110	16.4%
Age at CMA diagnosis (months) (median, IQR)	5.0	(3.0, 8.0)	5.0	(3.0, 8.0)
Weight at CMA diagnosis (kg) (median, IQR)	7.5	(6.1, 8.6)	7.4	(6.1, 8.7)
Weight at CMA diagnosis (SDS WHO) (median, IQR)	0.16	(-0.41, 0.69)	0.14	(-0.45, 0.79)
Length at CMA diagnosis (m) (median, IQR)	0.66	(0.61, 0.70)	0.66	(0.61, 0.70)
Length at CMA diagnosis (SDS WHO) (median, IQR)	0.05	(-0.76, 0.52)	-0.03	(-0.56, 0.94)
BMI at CMA diagnosis (kg/m^2) (median, IQR)	17.3	(16.2, 18.1)	17.2	(16.2, 18.1)
BMI at CMA diagnosis (SDS WHO) (median, IQR)	0.29	(-0.45, 0.73)	0.26	(-0.48, 0.66)
Positive prick by prick test for fresh milk	110/110	100.0%	110/110	100.0%
Positive skin prick test for α-lactoalbumin	96/110	87.3%	94/110	85.5%
Positive skin test positive for β-lactoglobulin	60/110	54.5%	70/110	63.6%
Positive skin prick test positive for casein	49/110	44.5%	51/110	46.4%
Gastrointestinal symptoms at CMA onset	61/110	55.5%	65/110	59.1%
Cutaneous symptoms at CMA onset	75/110	68.2%	73/110	66.4%
Respiratory symptoms at CMA onset	17/110	15.5%	14/110	12.7%

Slide 9

This figure depicted the main study outcome under complete case analysis. The results of this randomized, controlled trial show that the extensively hydrolyzed casein formula supplemented with the probiotic LGG is more effective than extensively hydrolyzed casein formula alone in preventing the occurrence of other allergic manifestations. The number of children needed to be treated with extensively hydrolyzed casein formula with the probiotic LGG to prevent the occurrence of at least 1 atopic manifestation during the 3-year follow-up is 4. All these data strongly support the beneficial effect elicited by this novel dietary strategy.

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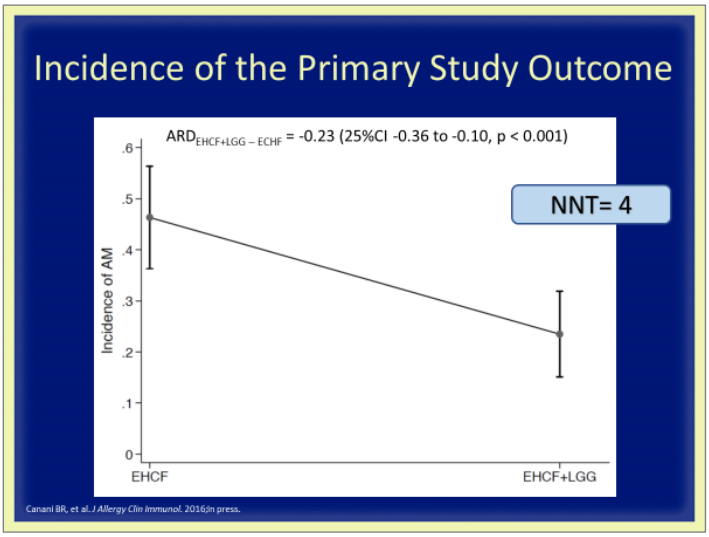
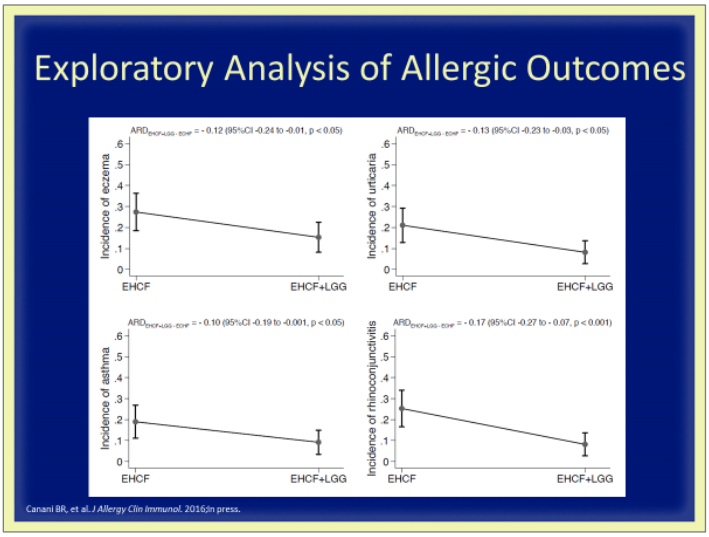


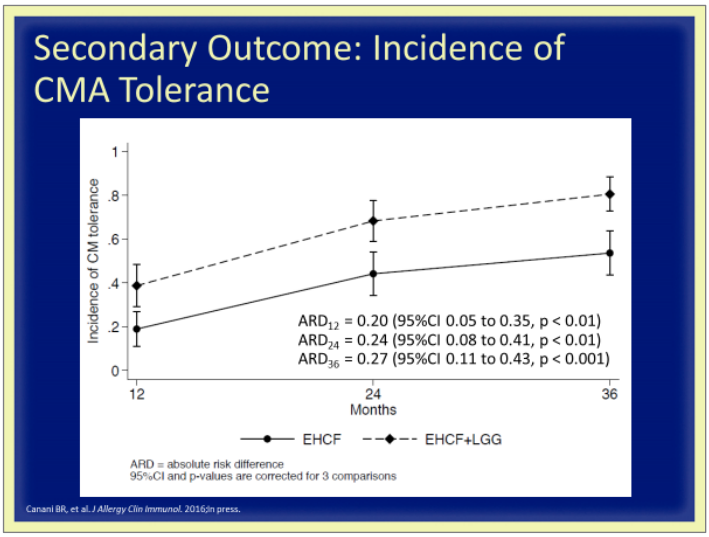
Slide 10

As you can see here in this slide [Slide 11], a similar trend was observed for all the components of the main study outcome, with significant absolute risk difference between the 2 groups, suggesting that this novel dietary strategy, based on extensively hydrolyzed casein formula with the probiotic LGG inside, is more effective than extensively hydrolyzed casein formula alone, at preventing the occurrence of eczema, asthma, urticaria and rhinoconjunctivits.



Slide 11

Additional evidence on the positive effects of this novel dietary strategy on oral tolerance acquisition has been provided in this study. As you can see here [Slide 12], at 12, 24 and 36 months of follow-up, an increased rate of children acquired an oral tolerance was observed in patients treated with extensively hydrolyzed casein formula with LGG. These data are of relevance considering the most recent evidence suggesting that the natural history of cow milk allergy has changed over time, with a higher proportion of children with disease persistence through 5 years of age and subsequent ages.



Slide 12

As you can see here [Slide 13], data on the skin prick test for whole cow milk paralleled that for tolerance acquisition, in fact, at 1 year, 2 years and 3 years of follow-up, patients treated with extensively hydrolyzed casein formula supplemented with LGG showed an increased rate of negativization of skin prick test.

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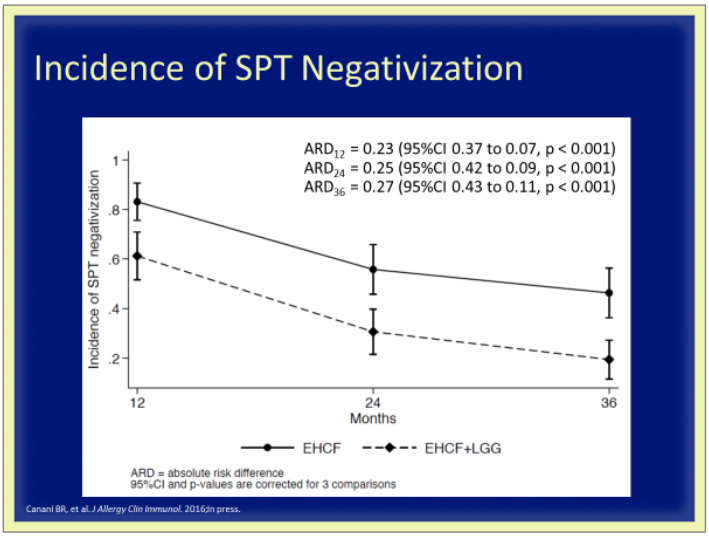
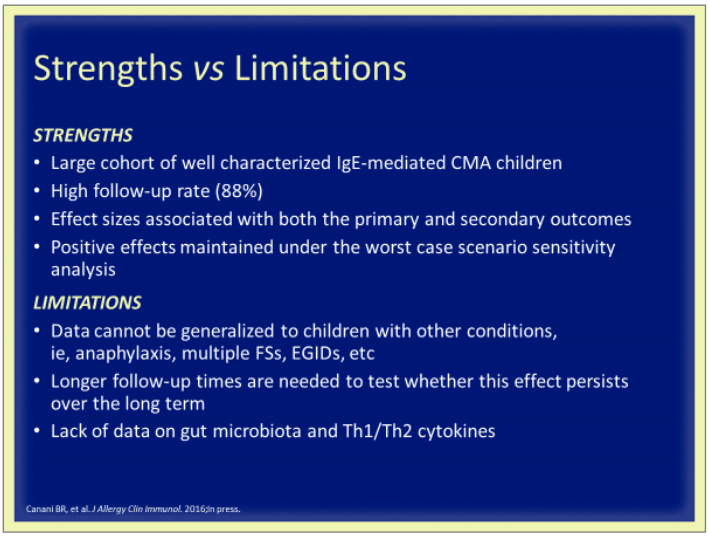


Slide 13

We guess that our study has several strengths. First of all, it is a randomized, controlled trial that was performed on a large sample of children with challenge-proven diagnosis of cow milk allergy followed at a tertiary center for pediatric allergy with a high follow-up rate.



Slide 14

Second, the effect size associated with both the primary and secondary outcomes were clinically relevant. Third, such effect size maintained a clear trend toward benefit under the worst case scenario sensitivity analysis.

However, as expected, our study has some limitations. First of all, our data cannot be generalized to children with conditions that were reasons for exclusion from the study, for example, anaphylaxis. The effect of extensively hydrolyzed casein formula supplemented with LGG vs extensively hydrolyzed casein formula alone, in these children, will have to be addressed by future studies.

Second, although our results showed that this novel strategy reduced the incidence of other allergic manifestations and favors the development of oral tolerance in children with IgE-mediated cow milk allergy after 1 year, 2 years and 3 years of data, longer follow-up times are needed to test whether this effect persists over the long term.

Third, our results are limited by the lack of data on gut microbiota and Th1/Th2 cytokine expression which would be useful to investigate the mechanisms by which the extensively hydrolyzed casein formula supplemented with LGG can produce its effect.

So, we can conclude that our active approach is to counteract, step by step, all factors involving cow milk allergy pathogenesis, modulating the interaction along dietary factors, gastric microbiota composition and function, epigenetic mechanism and immune system activity. And what we found is that extensively hydrolyzed casein formula supplemented with probiotic LGG is very active on all these pathways. The final results of this modulation is a down-regulation of allergic response and this positive mechanism drive to faster acquisition of oral tolerance and has sustained protection against other allergic manifestations in children affected by cow milk allergy.

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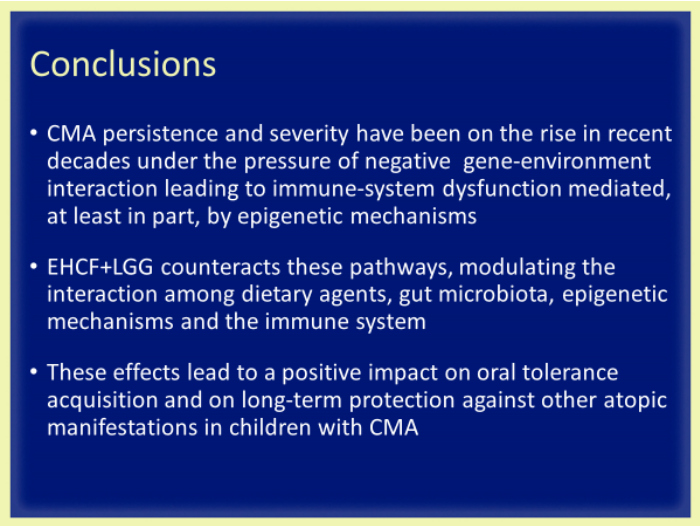

Slide 15

Question & Answer

Are there any data that suggest dysregulation of the microbiota in infants who later develop CMA?

Dr. Canani: Yes, so we have evidence suggesting that gut dysbiosis precede the cow milk allergy and influences during the early life, the subsequent development of other allergic conditions. In fact, it has been shown that some alteration in gut microbiota composition and function in the first month of life, the so-called dysbiosis, correlates with subsequent occurrence of food allergy in later years, suggesting that early gut dysbiosis contributes to subsequent development of food allergy. There are epidemiological studies that have established a clear correlation between factors that disrupt—that modify the gut microbiota composition during childhood—and immune conditions later in the life. Several factors are responsible for dysbiosis being associated with the occurrence of a food allergy, such as, for example, cesarean delivery, lack of breast milk, drugs used—mainly antibiotics and acidic inhibitors—antiseptic agents used, and the low-fat or high-fat diet. It has been demonstrated that neonatal antibiotic treatment reduces the microbial diversity and bacterial load and enhances food allergy sensitization. In fact, maternal use of antibiotics before or during pregnancy, as well as antibiotic courses during the first month of life, have been associated with an increased risk of cow milk allergy in infants.

Did you find any differences in weight gain or growth between the infants who received LGG and those who didn't?

Dr. Canani: No, we didn't observe a difference comparing body growth rate in children treated with extensively hydrolyzed casein formula supplemented with LGG or with extensively hydrolyzed casein formula alone. The changes in body weight and length or height were similar in the 2 groups.

Should extensively hydrolyzed formula be used prophylactically in infants with a sibling who developed cow's milk allergy?

Dr. Canani: Yes, there is evidence suggesting that in not breastfed babies, a possible cow milk allergy prevention strategy could be based on the use of extensively hydrolyzed casein formula. But, you know, it is a very dynamic field and more studies are necessary to better define the potential of this strategy on the use of extensively hydrolyzed casein formula supplemented with LGG on cow milk allergy prevention.

There was a similar study in JACI several years ago that showed a combination of *Lactobacillus casei* and *Bifidobacterium* did not improve tolerance to cow's milk allergy and this was surprising to me because I thought combinations of probiotics would be more likely to have an effect. Now, I also know there is a variability in individual formulations of EHF and probiotics. Given the results of your study and this other study, do you think there's something

specific for *Lactobacillus* GG or could the effect on tolerance be dependent on the specific combination or preparation of probiotic and EHF?

Dr. Canani: Yes, it is now clear that the many effects of probiotics on the immune system are strain-specific. Studies conducted with other *Lactobacillus* species did not obtain comparable results. Thus, if you want to target the immune system of a baby affected by cow milk allergy, for example, using a probiotic, it is important to be prudent in using only selected probiotic strains at a particular dose. In particular, the specificity of LGG, is related, at least in part, to the fact that this particular probiotic is able to produce more than 300 strain-specific peptides and that particular DNA sequence that are recognized by our immune system and promote an anti-allergic response. In addition, we know now that LGG is able to shape gut microbiota composition, in fact, increasing the number of butyrate-producing bacteria strains that regulates positively the mechanism of immune tolerance. And, we feel that our results could derive, at least in part, by this nice mechanism of action exhibited by LGG and direct effect or more casein derived at the time on our immune system.