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# **Is Probiotic Supplementation Effective In Reducing The Incidence Of Atopic Dermatitis In Children Age 3 And Under?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

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Philadelphia, Pennsylvania

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## ABSTRACT

**OBJECTIVE:** The objective of this selective EBM review is to determine whether or not probiotic supplementation is effective in reducing the incidence of atopic dermatitis in children age 3 and younger.

**STUDY DESIGN:** Systematic review of three English language primary studies one published in 2009 and the other two in 2010.

**DATA SOURCES:** Three double blind randomized controlled trials comparing the efficacy of probiotic supplementation for reducing the incidence of atopic dermatitis in children ages 3 and under were found using Cochrane Library EBM and PubMed databases.

**OUTCOMES MEASURED:** Diagnosis of atopic dermatitis, via a positive skin-prick-test result or elevated specific immunoglobulin E [IgE] level , Atopic dermatitis severity using SCORAD scores pre/post intervention , and parental reported weekly diaries of the health status subjects, a British Medical Research Council questionnaire and the Dutch European community Respiratory Health Survey.

**RESULTS:** Minimal intervention-related adverse events were reported in the studies, and included feeding problems, formula intolerance, and the need for corticosteroid treatment. Niers et al showed in the first 3 months, parental reported incidence of atopic dermatitis was significantly lower in the probiotic group 6/50 compared to the placebo group 15/52, and  $p=0.035$ . Gruber et al demonstrated after 1 year, atopic dermatitis occurred in fewer infants from the probiotic group, (5.7%) than from the control group (9.7%),  $p=0.04$  and CI is 95% and is narrow. Dotterud et al demonstrated at 2 years of age, probiotic intervention group showed 29/138 subjects were assessed as having atopic dermatitis (21%). In the placebo group 48/140 were assessed as having atopic dermatitis (34.3%). The Odds ratio of the cumulative incidence of atopic dermatitis was calculated to be 0.51 and the p value was equal to 0.013. The p value calculated determined that the incidence of atopic dermatitis in the probiotic group versus the placebo group was statistically significant ( $p<0.05$ ).

**CONCLUSION:** All three studies showed that probiotic supplementation is effective in reducing the incidence of atopic dermatitis in children age 3 and under.

**KEY WORDS:** atopic dermatitis, probiotics, pregnancy, children, infant atopic dermatitis

## INTRODUCTION

Atopic dermatitis is a chronic, inflammatory skin condition with prevalence rising in many industrialized countries.<sup>5</sup> Symptoms include erythema, scaling and pruritus in affected areas, and often result in sleeplessness, psychological stress, poor self-esteem, anxiety, and poor school or work performance.<sup>2</sup> This paper evaluates three double blind randomized controlled trials comparing the efficacy of probiotic supplementation for reducing the incidence of atopic dermatitis in children ages 3 and under.

Atopic dermatitis is the most common inflammatory skin disease in infancy. Unfortunately, incidence has increased steadily in the industrialized countries over the last 3 decades and affects 10% to 20% of children.<sup>2</sup> The disease often presents in early childhood and persists into adult life in 60% of patients.<sup>3</sup> In the U.S. cost of atopic dermatitis treatment is estimated to be 0.9 to 3.8 billion dollars every year, with direct medical costs and out-of-pocket expenses averaging \$609/patient/year.<sup>2</sup> Atopic dermatitis is responsible for countless medical office visits.<sup>2</sup> Atopic dermatitis adds to childhood morbidity and prevalence of allergic disease has increased in the past few decades.<sup>5</sup> Hygiene hypothesis suggests increased prevalence is associated with reduced exposure to microbial components early in life.<sup>6</sup>

Current treatment of atopic dermatitis includes skin hydration, emollients, avoidance of allergens and irritants, and use of antihistamine drugs or corticosteroids during exacerbations.<sup>5</sup> The peak incidence of atopic dermatitis is in the first year of life.<sup>5</sup> Positive family history is the strongest predictor for the development of atopic dermatitis but majority of children who express atopic disease have a negative family history.<sup>5</sup> Allergic disease has been associated with altered intestinal micro biota,<sup>4</sup> which plays an

important physiological role in the postnatal development of the immune system.<sup>5</sup>

Probiotics have been suggested as a potential treatment for atopic dermatitis and may be a potential approach for prevention of this hard to treat skin condition.<sup>6</sup>

## OBJECTIVE

The objective of this selective EBM review is to determine whether or not probiotic supplementation is effective in reducing the incidence of atopic dermatitis in children age 3 and younger.

## METHODS

A number of criteria were considered in the selection of utilized studies. Only double blind randomized controlled trials that introduced probiotic supplementation compared to placebo were considered. The population was limited to children under 3 years of age. The following probiotic interventions were deemed acceptable: *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *La-5*, *Bifidobacterium animalis subsp lactis Bb-12*, nonhydrolyzed cow's milk with short and long chain oligosaccharides (ratio 9:1, 85% of mixture) and pectin derived acidic oligosaccharides (15% of mixture), *Bifidobacterium bifidum*, *Bifidobacterium lactis*, and *Lactococcus lactis*. Outcomes of interest included, positive skin prick test results for elevated specific immunoglobulin E for atopic dermatitis, SCORAD scores, weekly parent diaries documenting atopy related symptoms and doctor visits. SCORAD is a clinical tool used to assess the extent and severity of atopic dermatitis (SCORing Atopic Dermatitis) prior to and post treatment to determine effectiveness.

A detailed search was performed by the author of this review between January of 2012 and February of the same year. The online search was completed using Cochrane Library EBM Database and PubMed Online with the key words “atopic dermatitis,” “probiotics,” “pregnancy,” “children,” and “infant atopic dermatitis.” All three articles that were selected to be included in this review were written in the English language and published in peer-reviewed journals from 2009 until present. A Cochrane Meta Analysis titled “*Probiotics for treating eczema*” was performed in 2008 but was not included in this meta-analysis and all articles used were published after 2008. An additional meta-analysis titled “*Meta analysis of lactic acid bacteria as probiotics for the primary prevention of infantile eczema*” was published by Zhu DL and Yang, W, H. in 2010 on PubMed. No information from this meta-analysis will be used as part of this paper. Selection of studies was based on relevance to the topic of interest and only studies that reported patient oriented outcome (Patient Oriented Evidence that Matters, or POEMS) were included. Inclusion criteria for all chosen literature included studies focusing on children up to the age of 3. Exclusion criteria included children over the age of 3, children whose mothers took antibiotics during breast feeding or in the first 2 weeks of the child’s life, mothers who had been taking probiotic supplements during the last 4 weeks, mothers who were Hepatitis B, HIV, and Group B strep positive during pregnancy, children with feeding problems or difficulty ingesting the study product, and infants with known congenital disease that could interfere with the study. The studies either reported p values or contained dichotomous data, which could be used to calculate Relative Risk Reduction/Increase (RRR/RI), Absolute Risk Reduction/Increase (ARR/ARI) and

Numbers Needed to Treat/Harm (NNT/NNH). Demographics of the three final selection are reported and displayed in Table 1.

TABLE 1: Demographics & Characteristics of included studies

STUDY	TYPE	# PTS.	AGE	INCLUSION CRITERIA	EXCLUSION CRITERIA	W/D	INTERVENTIONS
Dotterud <sup>1</sup> (2010)	Randomized double-blind, placebo-controlled study	278	Up to 2 years of age	278 infants (138 mothers on probiotics, 140 mother's on placebo) pregnant women who were planning to breastfeed during the first 3 postnatal months, were in week<36 of pregnancy, liked and tolerated fermented milk and were not at risk of developing pregnancy complications such as pre-eclampsia.	Women who had been taking probiotic supplements during the last 4 weeks or were planning to move away from study location.	65	Women were given 250 mL of probiotic milk or placebo milk per day from 36 weeks' gestation to 3 months after delivery while breastfeeding. The probiotic milk contained Lactobacillus rhamnosus, Lactobacillus acidophilus La-5, and Bifidobacterium animalis subsp lactis Bb-12
Gruber <sup>5</sup> (2010)	Double blind, randomized placebo controlled study	1130	Up to 1 year of age	Term weaned infants younger than 8 weeks without a family history of atopic dermatitis from northern Europe. Healthy term infants (gestational age 37-42 weeks) with a normal birth weight (>10 <sup>th</sup> percentile and <90 <sup>th</sup> percentile for gestational age, age up to 8 weeks when entering the study, without a positive history of allergic disease of a parent/sibling and without metabolic disorder requiring special diet.	Mother with hepatitis B, HIV, group B strep during pregnancy; moms taking ABX during breast-feeding; infants with known congenital disease that could interfere with the study;	129	Infants in the probiotics group received a nonhydrolyzed cow's milk-based formula with a specific mixture of short- and long-chain oligosaccharides (ratio 9:1, 85% of mixture) and pectin-derived acidic oligosaccharides (15% of mixture). The PG and CG received a starter formula for the first 6 months of life, and then a follow-on formula was offered.
Niers <sup>6</sup> (2009)	Double blind, randomized placebo controlled study	156	Up to 24 months	156 pregnant women with a positive family history of allergic disease and their offspring Women recruited at least 2 months before delivery	Children were excluded if their mother received ABX treatment in the first 2 weeks of life, if ingestion of the study product was difficult because of vomiting or feeding problems for longer than 3 weeks from birth, or any medical problems.	54	Prenatal administration of a mixture of probiotic bacteria (Bifidobacterium bifidum, Bifidobacterium lactis, and Lactococcus lactis) to mothers of high-risk children and postnatal supplementation to their offspring for the first 12 months of life.

## OUTCOMES

The outcomes measure were those of patient oriented evidence that matters (POEMS), which includes incidence of atopic dermatitis. Niers, et al. measured pre- and postnatal supplementation of probiotic bacteria and its prevention of atopic dermatitis in high risk children for the first 24 months of life.<sup>3</sup> The study measured the outcomes by a variety of methods including parental reported weekly diaries of the health status of their child, any doctor visits, symptoms and complaints of eczema.<sup>3</sup> A British Medical Research Council questionnaire and the Dutch European community Respiratory Health Survey was distributed to parents in the study to evaluate participants for symptoms at the age of 3, 12, and 24 months.<sup>3</sup> Study subjects received a physical examination and evaluation by a study blinded physician at ages 3, 12, and 24 months.<sup>3</sup> Parental reported eczema and physician diagnosed eczema was defined as noninfectious dermatitis with typical features such as redness, dryness, edema, oozing, itching, scratching and distribution.<sup>3</sup> Dotterud, et al. measured if infants whose mothers ingested probiotic milk before birth and during breastfeeding were able to prevent allergic disease in the first 2 years of life compared to infants whose mother's ingested placebo milk.<sup>1</sup> In order to measure the outcome, at 2 years of age, all children were assessed for diagnosis of atopic dermatitis, via a positive skin-prick-test result for elevated specific immunoglobulin E [IgE] level.<sup>1</sup> Gruber, et al. addressed if supplementation of prebiotics and immunoactive oligosaccharides prevent the development of atopic dermatitis in infants through the first year of life.<sup>2</sup> Outcomes were measured through Atopic dermatitis being diagnosed according to standard criteria based on the typical



morphology and distribution of skin lesions, pruritus, and chronicity with a duration of at least 14 days and or chronically relapsing.<sup>2</sup> SCORAD scores. T-helper 2-specific thymus and activation- regulated chemokine levels, total immunoglobulin E levels, and percentage sensitized to hen's egg or cow's milk.<sup>2</sup>

## RESULTS

Three double blind randomized controlled trials are analyzed in this review. All participants observed for incidence of atopic dermatitis are 3 years of age or younger and were introduced to probiotic treatment either directly through formula or prenatally through ingestion by their mothers. All studies used blinded participants receiving probiotic supplementation and were measured against a blinded placebo control group. Results of all three studies supported supplementation with probiotics as an effective means to prevent atopic dermatitis in children under the age of 3. The results were presented in dichotomous form in the Gruber, et al.<sup>2</sup> and Dotterud, et al.<sup>1</sup> and the Niers, et al. study<sup>3</sup>.

The Dotterud, et al. study assessed if probiotics given to pregnant women in a nonselected population could prevent atopic dermatitis during the child's first 2 years of life.<sup>1</sup> Women received probiotic milk containing *Lactobacillus rhamnosus GG*, *L. acidophilus La-5* and *Bifidobacterium animalis subsp. Bb-12* or placebo milk from 36 weeks gestation to 3 months postnatally during breastfeeding.<sup>1</sup> At 2 years of age, 138 children in the probiotic group and 140 children in the placebo group of the study were assessed for atopic dermatitis. Of those children in the probiotic group, 29 subjects of the 138 were assessed as having atopic dermatitis for a total of 21%. (See Table 2) Of those children in the placebo group, 48 subjects of the 140 were assessed as having atopic

dermatitis for a total of 34.3%. (see Table 2) The Odds ratio of the cumulative incidence of atopic dermatitis was calculated to be 0.51 and the p value was equal to 0.013. The p value calculated determined that the incidence of atopic dermatitis in the probiotic group versus the placebo group was statistically significant ( $p < 0.05$ ).

TABLE 2: Cumulative incidence of atopic dermatitis among 2 year old children in the probiotic group and placebo group reported by Dotterud, et al.

# of participants in probiotic group, n	# of participants in placebo group, n	Probiotic group with AD	Placebo group with AD	% of Probiotic group with AD	% of Placebo group with AD
n=138	n=140	n=29	n=48	21%	34.3%

The control event rate (CER) was determined as those children at 2 years of age diagnosed with atopic dermatitis who were not receiving probiotic supplementation. The CER was calculated to be 34.3%. The experimental event rate (EER) was determined as the number of children at 2 years of age who had diagnosed atopic dermatitis and were receiving probiotic supplementation. The EER was found to be 21%. From this data, the relative risk reduction (RRR) was calculated to be 0.133 with a number needed to treat (NNT) of 8. Therefore for every 8 children who were treated with probiotics there was one fewer incidence of atopic dermatitis in the control group of children not taking probiotics.<sup>1</sup>

The Gruber, et al. study assessed if supplementation of prebiotics and immunoactive oligosaccharides in infants reduces the incidence of atopic dermatitis in the first year of life.<sup>2</sup> Healthy term infants from 5 European countries with low risk of atopic dermatitis were randomized to a prebiotic group and a control group. A total of 414 infants received a specific mixture of neutral oligosaccharides and pectin-derived acetic

acid oligosaccharides probiotic formula while 416 infants received a placebo formula. Atopic dermatitis was diagnosed by a physician according to standard criteria based on distribution of skin lesions, pruritus, and duration of at least 14 days or chronic relapse. Within the first year of life, atopic dermatitis occurred in statistically significant fewer infants from the prebiotic group, (5.7%) than from the control group (9.7%),  $p=0.04$  and CI is 95%, lower value of 13 and upper value of 386 and is narrow<sup>2</sup> (see Table 3)

The control event rate (CER) was determined as those children at 1 year of age diagnosed with atopic dermatitis who were not receiving probiotic supplementation. The CER was calculated to be 9.7%. The experimental event rate (EER) was determined as the number of children at 1 year of age who had diagnosed atopic dermatitis and were receiving probiotic supplementation. The EER was found to be 5.7%. From this data, the relative risk reduction (RRR) was calculated to be 0.41 with a number needed to treat (NNT) of 25. The incidence of atopic dermatitis was significantly lower by 44% in the prebiotic group versus the control group. The number needed to treat to prevent 1 case of atopic dermatitis by supplementation of probiotics was 25 infants.

TABLE 3: Incidence of atopic dermatitis in probiotic infants VS. placebo in the first year of life reported by Gruber, et al.

	# of infants, n	Incidence of atopic dermatitis	% of infants with atopic dermatitis	% of Probiotic group with AD
probiotic group	n=414	n=24	5.7%	21%
placebo group	n=416	n=40	9.7%	21%

The Niers, et al. study assessed prenatal and postnatal supplementation of probiotic bacteria prevent allergic disease in high risk children in the first year of

life.<sup>3</sup> A probiotic bacteria mixture of *Bifidobacterium bifidum*, *Bifidobacterium lactis*, and

Study	CER	EER	RRR	RRR	NNT	P value CI
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*Lactococcus lactis* were prenatally administered to mothers of high-risk children and to their offspring for the first 12 months of life. Originally 156 mothers were enrolled in the study but 54 of the participants met the exclusion criteria. (see Table 1) During the first 3 months of the study, a total of 50 infants received the probiotic mixture and 52 infants received the placebo mixture. The number of infants in the placebo group fell to 48 infants after 3 months and a total of 48 infants remained in the placebo group for 2 years. Dropout was due to motivational problems and the intervention group number remained at a constant 50 participants throughout the study. In the first 3 months, parental reported incidence of atopic dermatitis was statistically significantly lower in the probiotic group 6/50 compared to the placebo group 15/52, and  $p=0.035$ . (see Table 4) Incidence of parental reported atopic dermatitis at year 1 was 23/50 for probiotic group and 31/48 in the placebo group. At 2 years, the incidence of atopic dermatitis rose to 27/50 in the probiotic group and 34/48 in the placebo group. The number needed to treat was 5.9 at ages 3 and 12 months and increased to 6.7 at age 2 years. (see Table 5)

Table 4: Incidence of atopic dermatitis in the probiotic group and placebo group during the first w years of life as reported by Niers, et al.

Time	Infants with AD with probiotic intervention	Infants with AD with placebo intervention
3months	6/50 (12%)	15/52 (28.8%)
1 year	23/50 (46%)	31/48 (64.6%)
2 years	27/50 (54%)	34/48 (71%)

Table 5: Efficacy of probiotics in prevention of Atopic Dermatitis (Dotterud et al, Gruber et al, Niers et al)

Dotterud, et al.	34.3%	21%	38.7%	13.3%	8	p =0.013 CI:95%
Gruber, et al	9.7%	5.7%	41%	4%	25	p = 0.04 CI: 95%
Niers, et al	21%	6%	-71%	-15%	-7	P=0.021 CI: 95%

Because of the treatments analyzed in these studies, the safety of the patients involved was closely monitored throughout the trials. Since all three trials were measuring incidence of atopic dermatitis in a probiotic fed group versus a placebo fed group, the worst adverse event experienced was atopic dermatitis or intolerance to probiotic or placebo formula. Gruber, et al. reported 17 patients withdrew from the study due to formula intolerance and 56 patients received corticosteroid treatment for severe atopic dermatitis.<sup>2</sup> Niers, et al. reported 2 participants withdrew from the study due to feeding problems.<sup>3</sup> Dotterud, et al reported no adverse events during the study.<sup>1</sup> (See Table 6)

Table 6: Adverse Events Across Trials (# of patients monitored)

	Dotterud et al( 278 )	Gruber et al(1130 )	Niers et al (156)
Adverse Event			
Feeding Problems			2
Formula Intolerance		17	
Corticosteroids		56	

## CONCLUSION

The combination of probiotic bacteria used shows a preventative effect on the incidence of atopic dermatitis in high risk children, which seems to be sustained during the first 2 years of life.<sup>3</sup> In analyzing the results, the preventative effect appears to be established within the first 3 months of life.<sup>3</sup>



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